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Catabolic effect of dexamethasone in the preterm baby

K G Brownlee, P C N[illegible] Henderson, M Smith, J H Green, P R F Dear

Abstract

Most babies treated with dexamethasone for bronchopulmonary dysplasia exhibit an appreciable rise in the blood urea concentration, from a mean of 2·3 mmol/l before steroid to a mean of 7·1 mmol/l after. In order to discover whether this was primarily the result of increased protein catabolism, nitrogen balance studies before and after the start of dexamethasone were performed and a mean deficit in nitrogen retention of 158 mg/kg/24 hours was found. Similarly the urinary 3-methylhistidine (3MH):creatinine ratio before and after the commencement of dexamethasone treatment in a group of preterm babies was measured. It was found that there was a substantial increase in 3MH excretion after dexamethasone: from a mean 3MH:creatinine ratio of 46 in the week before steroids to a mean ratio of 77 in the week after. As 3MH emanates almost exclusively from the breakdown of actin in skeletal muscle cells, this finding implies the loss of muscle tissue. It was also found that the babies were in less positive nitrogen balance after dexamethasone, to a degree which is significant relative to their protein reserves. The long term consequences of a period of increased catabolism are not yet known but the authors suggest caution in the use of dexamethasone, at least in babies with milder degrees of bronchopulmonary dysplasia in whom the ratio of benefit to risk may be less favourable.

Corticosteroid treatment is now an established part of the management of bronchopulmonary dysplasia. While large, multicentre, research studies will hopefully continue to define the precise indications for the use of steroids, numerous informal 'studies' are being conducted in individual units. The decision to use steroids will be based on a clinician's perception of the risk:benefit ratio in an individual case. As it is likely that there will be a move towards using corticosteroids earlier in the course of the disease and in less severe cases (as seems an inevitable phase in the evolution of any effective drug treatment) more information about the risks must be sought so that the risk:benefit ratio can be evaluated as accurately as possible.

A striking phenomenon that we have observed in almost all dexamethasone treated preterm babies is a sharp rise in the blood urea concentration. This usually begins within 48 hours of starting the drug and lasts for a week or so. As dexamethasone is well known to increase protein catabolism in adults,[1] we thought that this was the most likely explanation for the observation. As any increase in protein catabolism in a sick preterm baby with poor nutritional reserves and limited renal function is potentially very harmful, we have investigated the effect further.

In order to see if there was evidence of increased protein catabolism we performed nitrogen balances before and during dexamethasone treatment of 11 infants. In order to see if there was evidence of catabolism of endogenous structural protein, as distinct from dietary protein, we also studied the urinary excretion of 3-methylhistidine (3MH). 3MH results from the methylation of the amino acid histidine and its sole source in the newborn infant is the protein actin.[2, 3] The vast majority of actin is to be found within skeletal muscle (the 3MH concentration in skeletal muscle being at least 10 times that in other tissues), but small amounts are found in other cell types. 3MH is released when actin is broken down. It is not metabolised in man and is fully excreted in the urine. As, in the absence of meat from the diet, creatinine is excreted in proportion to the skeletal muscle mass, the urinary 3MH:creatinine ratio should be proportional to the fractional degradation rate of myofibrillar protein. The 3MH:creatinine ratio has been found to correlate well with nitrogen balance in preterm infants,[4] and several authors have used 3MH excretion to quantify protein turnover and muscle breakdown in adults and neonates, in relation to nutritional state, surgery, and trauma.[5–7] In animals, 3MH excretion has been used to demonstrate a rise in protein catabolism after dexamethasone treatment.[8]

Patients and methods

Four groups of babies were investigated.

GROUP 1

In this group of 11 babies full nitrogen balance studies were performed before and after the start of steroids. Boys were selected because of the relative ease of collecting complete urine specimens. Twenty four hour balance studies were conducted immediately before the start of steroids and again on the third day of treatment. All of the babies were parenterally fed and none produced any stools during the balance studies.

GROUP 2

In order to examine the day to day variation in the 3MH:creatinine ratio, and the reproduci-

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bility of the measurement method, we obtained urine specimens from 10 preterm babies who were healthy and growing normally on full milk feeds. Five specimens were collected from each baby over a two week period.

GROUP 3

This group comprises 34 babies treated with dexamethasone for bronchopulmonary dysplasia during a three year period (1987–9). Each had received a three week course of dexamethasone: 0·6 mg/kg/day in the first week, 0·3 mg/kg/day in the second week, and 0·15 mg/kg/day in the third. Specimens for blood urea and creatinine concentration were collected daily for one week before steroids were started and for as long as five weeks after.

GROUP 4

In this group of 11 babies, analysis of the urinary 3MH:creatinine ratio was undertaken in addition to measurement of the blood urea and creatinine, before and after dexamethasone treatment. Urine samples were collected on alternate days for a week before starting steroids and for two weeks after steroids were started.

All babies in group 1, 3, and 4 were in a stable condition before steroids were started and sepsis was excluded throughout by daily C reactive protein estimations, and blood cultures where appropriate. All were well hydrated with a minimum fluid intake of 165 ml/kg/day (range 165–200 ml/kg), and the fluid intake was not altered during the course of dexamethasone treatment. None of the babies was treated with diuretics and none had evidence of a patent ductus arteriosus.

Urinary nitrogen estimations were performed by the Kjeldahl method, using a Kjeltec Auto 1000 analyser with an analytical coefficient of variation of <2% for eight repeat samples. Urea and creatinine estimations were made using a Beckman, Astra 8, Clinical Chemistry Analyser. Urinary 3MH was measured using a Chromaspek M automated, ion exchange amino acid analyser (Hilger Analytical).

Statistical comparisons between sets of normal data were performed using paired Student's *t* tests, and between sets of non-normal data by the Mann-Whitney U test.

The study had the approval of the local research (ethics) committee and the parents of the babies.

Results

GROUP 2

The median gestational and postnatal ages of the 10 babies in group 2 were 33·4 weeks (range 31–35) and 14·2 days (range 7–29) respectively. Fifty urine samples were obtained from the babies in group 2. The 3MH:creatinine ratios of these samples were normally distributed about a mean (SD) of 38·3 (11·0) mmol/l. The laboratory reproducibility of results had an error of <5%.

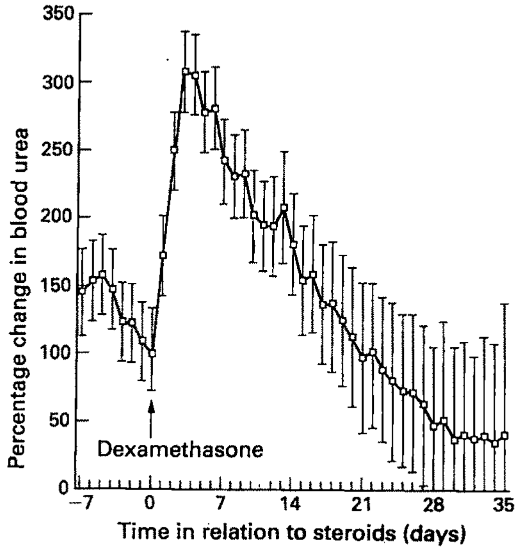

Figure 1 Percentage change in blood urea concentration plotted against time (days) in relation to the start of steroid treatment. Bars show 95% confidence intervals.

GROUPS 3 AND 4 COMBINED

The babies in groups 3 and 4 were combined for the analysis of the blood urea and creatinine concentrations after dexamethasone. This gave a total of 45 babies. The median gestation for this group was 27 weeks (range: 24–31 weeks). The median age at the start of steroid treatment was 18 days (range : 7–71 days). The blood urea data are shown in fig 1. The day before dexamethasone was started the mean (SEM) blood urea was 2·3 (0·28) mmol/l. The concentration then rose to a peak of 7·1 (0·43) mmol/l on the third day after starting dexamethasone. This was followed by a gradual decline, such that by the end of the three week course the concentration was approximately the same as it had been before treatment.

Figure 2 illustrates the percentage change in the blood creatinine concentration in relation to dexamethasone treatment. It can be seen that the blood creatinine was falling before dexamethasone was started and that trend continued, uninterrupted, after the start of dexamethasone.

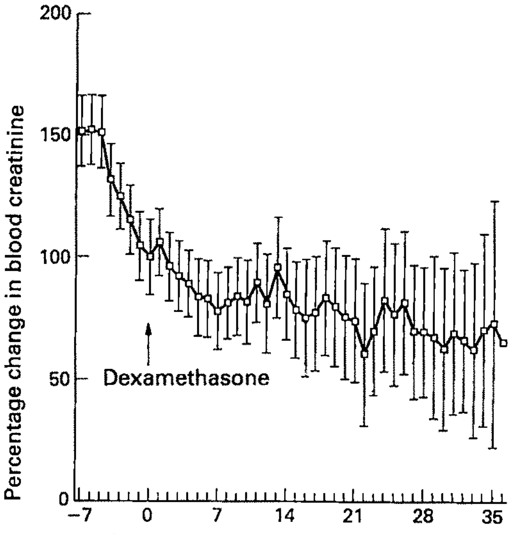

Figure 2 Percentage change in creatinine concentration plotted against time (days) in relation to the start of steroid treatment. Bars show 95% confidence intervals.

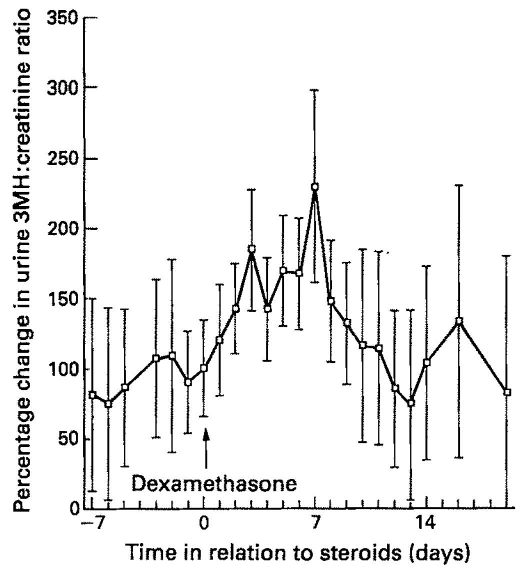

Figure 3 Percentage change in urine 3MH:creatinine ratio plotted against time (days) in relation to the start of steroid treatment. Bars show 95% confidence intervals.

GROUP 4

The 11 babies in group 4 were very similar to those in group 3. Their median gestational age was 27 weeks (range 24–31) and the median age at which steroids were started was 14 days (range 9–32). The mean blood urea concentration before dexamethasone was started was 2·6 mmol/l and this rose to a mean of 6·8 mmol/l by day 3.

Figure 3 shows the percentage change of urinary 3MH:creatinine ratio data plotted in relation to dexamethasone treatment. The mean value for the urinary 3MH:creatinine ratio in the week before starting steroids was 46 and this rose significantly to a mean of 77 in the first week after the start of steroids (p<0·0001). In the next week this ratio fell to a mean of 58, significantly less than the value in the first week of steroid treatment (p=0·01), but still significantly greater than the pretreatment value (p=0·03). By the third week of steroid treatment the 3MH:creatinine ratio had fallen to 53; this value was not significantly different from the pretreatment value (p=0·43).

Figure 4 shows the relationship between the urinary 3MH:creatinine ratio deviation from the patient mean and the blood urea deviation from the patient mean after the start of steroid treatment. There is a significant relationship between the two variables (r=0·5, p<0·0001).

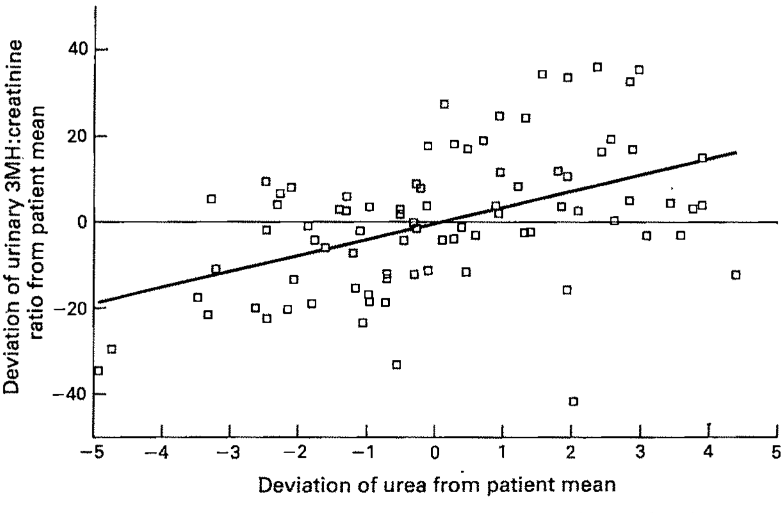

Figure 4 Deviation from patient mean of urine 3MH:creatinine ratio plotted against deviation from patient mean of blood urea concentration. Regression line shown.

Results of nitrogen balance studies. Results are nitrogen retention in mg/kg/24 hours

Patient No	*Before steroids*	*After steroids*
1	746	550
2	629	560
3	611	379
4	476	244
5	402	242
6	386	216
7	351	255
8	343	298
9	338	14
10	215	35
11	210	176

GROUP 1

The 11 babies in group 1 were similar to those in the other groups. The median gestational age was 26 weeks (range 24–31) and the median age at which dexamethasone was started was 19 days (range 8–29).

The results of the nitrogen balance studies are shown in the table. All babies were in positive nitrogen balance before steroids were started and remained so despite steroids. There was, however, a significant reduction in nitrogen retention to approximately half the presteroid value (p=0·0006, paired *t* test).

Discussion

This study was conducted in order to investigate the cause of the increase blood urea concentration that we had observed during steroid treatment in preterm babies. Although we suspected the cause to be increased urea production, two other theoretical possibilities had to be considered.

One possibility is that dexamethasone causes a diuresis, which results in contraction of the extracellular fluid volume and consequential rise in blood urea concentration—that is, a dehydration effect. There is evidence of a diuresis after dexamethasone treatment of bronchopulmonary dysplasia.[9] The workers who described it speculated that the improvement in pulmonary function which dexamethasone produces may relate to the removal of fluid from the lung. However, in order to explain such an increase in the blood urea as we observed the dehydration would have to be severe. The fluid intake throughout our study was substantial (median 180 ml/kg/day, range 165 to 200 ml/kg/day), there was no difference in daily urine output collected for the nitrogen balance studies before and during steroid treatment, and there was no clinical evidence of dehydration in any of the babies. There was also no coincidental increase in the serum creatinine, which would be expected with a significant degree of dehydration, and the urinary creatinine concentrations did not increase. We are confident, on this evidence alone, to conclude that dehydration was not the explanation for the rise in blood urea which we have documented.

The second possible explanation for a rise in blood urea would be a deterioration in renal function. We see no reason why this should have occurred and found no evidence for it. In particular serum creatinine concentrations did not increase along with the urea concentrations.

The data presented in this paper strongly suggest that the observed increase in blood urea concentration is due almost entirely to an increase in protein catabolism, resulting in the breakdown of structural protein and an increase in urea production. As the preterm baby's capacity to concentrate and excrete urea is relatively poor the result is an accumulation of urea in the blood.

The nitrogen balance data from the babies in group 1 demonstrate beyond doubt that dexamethasone causes increased protein catabolism. The mean deficit in nitrogen retention was 170 mg/kg/day after the administration of steroids and this is equivalent to 1 g of protein/kg/day. If it is assumed that between 12% and 14% of the newborn's weight gain is made up of protein[10] then 1 g of protein/kg/day represents 7–8 g/kg/day of body weight. This would represent half of a newborn's anticipated weight gain.

In group 4 babies we have also shown a significant rise in the urinary 3MH:creatinine ratio after dexamethasone treatment (fig 3) as well as a significant correlation between blood urea and urine 3MH:creatinine ratio ($r=0{\cdot}611$, $p<0{\cdot}0001$). This shows that the increase in urea production seen with dexamethasone is partly due to increased breakdown of skeletal muscle protein.

It is well established that increased circulating endogenous and exogenous glucocorticoids result in a loss of muscle protein in man and other animals,[11] and we were not surprised to find that there was a similar effect in the preterm infant. Although to the best of our knowledge, ours is the first primary evidence for this phenomenon which has been produced in the newborn. Dexamethasone is thought to exert its catabolic effect via type 2 corticosteroid receptors, stimulation of which results in an increase in the proportion of fat to lean body mass by reducing protein.[12]

The main concern raised by our data is the possibility that a period of increased catabolism, and therefore interruption of growth, at such a vulnerable time of life might have permanent adverse consequences for growth and development. Catabolism of muscle protein is of course not necessarily detrimental as it can probably be made up for later. It is in any case apparently not too serious for the muscles concerned with breathing as dexamethasone hastens weaning from the ventilator in almost all cases. The real worry is that the catabolic effect of steroids might also adversely affect brain growth, which is less likely to be fully recoverable. The recent work by Lucas *et al* showing that the quality of nutrition in the early weeks of life may influence later development must be taken very seriously.[13] The effect of steroids, given in the neonatal period, on neurological outcome has caused concern for some time,[14] and in the experimental animal an adverse effect of steroids on brain growth has been demonstrated.[15] [16] Behavioural changes, delayed maturation, and impairment of fine motor control have been reported in studies on rodents given steroids in the immediate postnatal period.[17]

As with any treatment that has a mixture of good and bad effects the decision to use steroids in a case of bronchopulmonary dysplasia must be on the basis of an appraisal of the risks and benefits as they seem to apply in an individual case. The data in this paper add to the risk side of the equation.

There may be ways to minimise the catabolic effects of corticosteroids. Obvious possibilities would include the use of a smaller dose of dexamethasone, an alternative route of administration, such as nebulisation directly into the lung which would enable smaller doses to be used or the use of different steroid altogether. Another approach might be to try to counteract the catabolic effect with an anabolic hormone such as insulin or an anabolic steroid. However, until fresh approaches are found we would advocate the continued use of dexamethasone in its present dose for cases of severe ventilator dependent bronchopulmonary dysplasia but urge caution in the extension of its use to less severe cases.

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Dexamethasone increases plasma amino acid concentrations in bronchopulmonary dysplasia

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Abstract

Nine ventilated low birthweight babies were treated with dexamethasone (0·6 mg/kg/day). Appreciable suppression of weight gain was accompanied by uraemia and significant increases in the concentration of all amino acids except phenylalanine, tyrosine, threonine, and glutamate. Ornithine, citrulline, alanine, glutamine, and cystine concentrations increased threefold or more. The findings could not be explained by changes in dietary intake and presumably reflect pronounced catabolism, though the effects of dexamethasone on intermediary metabolism and membrane transport could also play a part.

Dexamethasone is used increasingly to treat infants with bronchopulmonary dysplasia, principally to facilitate the withdrawal of mechanical respiratory support.[1,2] The precise mode of action of this drug in bronchopulmonary dysplasia is not clear, but lung compliance is known to increase, possibly through clearance of interstitial oedema. Treatment, which may be given for six weeks or more,[2] is usually accompanied by suppression of weight gain and uraemia, indicating the presence of catabolism.[3] The metabolic vulnerability of immature infants provided with protein in excess of growth requirements is well known,[4–7] but there are no data about the metabolic effects of high dose corticosteroid treatment in this group of patients. In this study we have measured the effect of dexamethasone on plasma amino acid concentrations.

Patients and methods

PATIENTS

The infants studied had been mechanically ventilated from birth. Table 1 gives the birth weight and gestational and postnatal age of each. Dexamethasone was used in the presence of radiographic abnormalities suggestive of chronic lung disease when conventional respirator weaning techniques had failed. The decision to treat was taken by the clinician responsible and no other experimental intervention to the standard nursery protocol was made. The dose of dexamethasone employed was 0·6 mg/kg/day in three divided doses given intravenously or orally.

FEEDING

The method of feeding was determined by each infant's clinical state and not regulated for the purpose of this study. None of the infants was completely enterally fed and all were receiving commercial parenteral nutrition solutions (Vamin Infant, Kabi Pharmacia, 10% dextrose ±20% Intralipid, Kabi Pharmacia), as a part or the whole of their nutrient intake. The parenteral nutrition regimens used in our nursery provide between 167 and 502 kJ/kg/day, depending on lipid tolerance, and amino acid intake is adjusted to constrain protein equivalent: energy ratio between 3·35 and 6·70 g/MJ. Enterally fed infants received low birthweight formula (Cow and Gate) or human milk when available. Total nitrogen and energy intakes were calculated from nursing records and manufacturers' compositional data. The nitrogen content of human milk was assumed to be 200 mg/100 ml, and the energy content 251 kJ/100 ml or 293 kJ/100 ml, depending on whether banked milk (a mixture of dripped and expressed milk) or mother's own milk respectively was used.

ANTHROPOMETRY

Weight (g) was measured daily when clinical state permitted, using an averaging electronic scale with resolution of 1 g and precision of ±4 g. Weight gain was calculated as the linear regression coefficient (slope) of these measurements on time (days). This was divided by body weight at the commencement of treatment for comparative expression in units of g/kg/day. Although such ratio 'correction' can lead to erroneous conclusions when comparison is made between infants of differing size, we made comparison only within subjects between treatment periods.

BIOCHEMICAL ANALYSIS

Heparinised venous blood samples (0·5 ml) were drawn before the first dose of dexamethasone and on one occasion between two and seven days later when a clinical indication

Table 1 Clinical characteristics of the infants studied

Patient No	Birth weight (g)	Gestation (weeks)	Postnatal age (days)
1	1041	29	16
2	664	24	32
3	2300	32	13
4	842	28	18
5	726	24	22
6	830	25	45
7	1048	26	31
8	918	26	17
9	715	27	22
Median	842	26	22

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for routine sampling arose. Plasma was separated immediately and frozen to −20°C. A 200 µl aliquot was deproteinised with 20 µl of 35% (w/v) sulphosalicylic acid after the addition of 200 µl of 250 µmol/l L-norleucine, which was used as an internal standard. The mixture was vortexed for a few seconds before incubating at room temperature for 5 minutes and then centrifuging again for 5 minutes at 15 850 *g*. An aliquot of 350 µl of the deproteinised supernatant was mixed with an equal volume of Beckman lithium diluent (ph 2·2) and the sample either stored at −60°C or filtered through a 0·22 µm filter for immediate analysis.

Amino acid concentrations were measured using a cation exchange high performance liquid chromatography (HPLC) system (Beckman System Gold) with postcolumn ninhydrin derivatisation, detecting primary amino acids and related compounds at 570 nm wavelength. The system was calibrated using a 250 µmol/l Beckman physiological standard. For each infant, specimens collected before and during treatment were analysed sequentially to ensure compatible measurement conditions. The precision (coefficient of variation) of the assay procedure was established by replicate assay (n=8) of the same sample of adult blood. It lay between 1·5 and 5·2% for all amino acids except citrulline (10·7%).

Plasma urea was determined by the urease method on a random access analyser in the hospital routine laboratory.

STATISTICAL ANALYSIS

The number of patients studied was small (n=9) and most variables did not appear normally distributed. Consequently the Wilcoxon signed rank test has been employed to make comparisons before and during treatment within infants. Two tailed probability estimates (p) are quoted throughout; values of <0·05 were deemed significant.

Results

NITROGEN AND ENERGY INTAKE DURING STUDY

Table 2 shows the average daily nitrogen and energy intake of each baby during the seven days before and the seven days after dexamethasone was commenced. These, and protein:energy ratio, did not differ significantly between the two periods (Wilcoxon signed rank test). There was a small difference in the ratio of enteral to parenteral intake between treatment periods: the median proportion of total fluid intake as milk before treatment was 26% (range 0–91%) and 19% (range 0–66%) during treatment. This difference was not significant (Wilcoxon signed rank test, p>0·1) and was attributable to interruption of enteral feeding on endotracheal extubation.

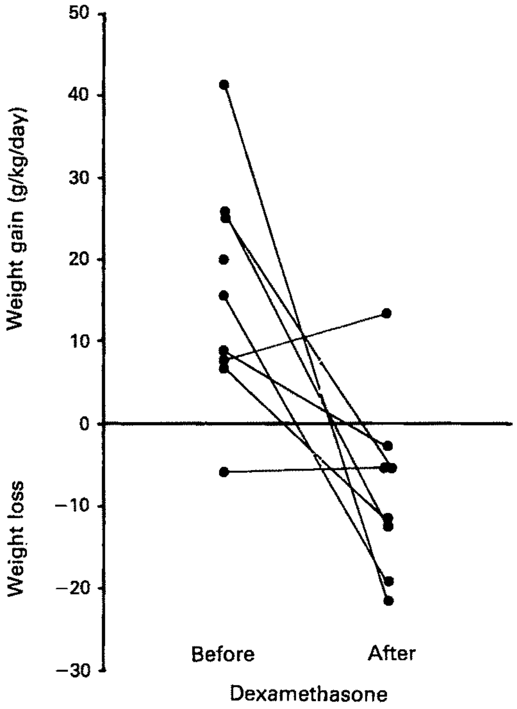

Figure 1 Weight gain (g/kg/day) during the week before commencing dexamethasone and during the first week of treatment.

WEIGHT GAIN

Figure 1 shows tied values for average daily weight gain or loss during the week before and the week after commencing dexamethasone treatment. In one case insufficient weight data were obtained during the second week to calculate rate of change. In six of the remaining eight cases there was a net weight loss on treatment. These changes were significant (Wilcoxon signed rank test, p<0·05).

PLASMA UREA CONCENTRATIONS

Figure 2 shows the distribution of plasma urea values with time. There was a clear increase in

Table 2 Nitrogen, energy intakes, and weight velocity of infants studied

Patient No	Before dexamethasone			After dexamethasone		
	Nitrogen intake (mg/kg/day)	*Energy intake (kJ/kg/day)*	*Weight velocity (g/kg/day)*	*Nitrogen intake (mg/kg/day)*	*Energy intake (kJ/kg/day)*	*Weight velocity (g/kg/day)*
1	246	368	−5·8	324	431	−5·2
2	350	439	6·9	36	401	−11·7
3	107	205	20·0	98	134	*
4	326	477	41·3	236	397	−21·2
5	356	418	26·0	259	380	−5·3
6	392	435	25·4	363	380	−12·3
7	293	330	8·8	449	531	−2·8
8	287	318	15·7	410	414	−19·1
9	289	405	7·7	330	410	13·4
Median	293	405	15·7	330	401	−8·5

*Denotes insufficient data to calculate velocity.

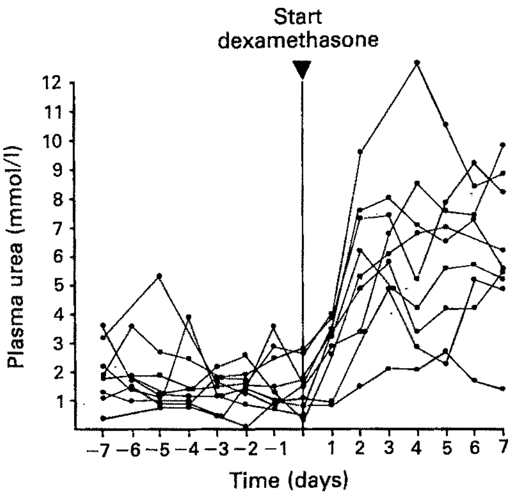

Figure 2 Plasma urea values (mmol/l) during the week before commencing dexamethasone and during the first week of treatment.

both the median plasma urea concentration and variability between individuals during treatment.

PLASMA AMINO ACID CONCENTRATIONS

Table 3 shows the median concentration (with range) for each amino acid before and after treatment. Significant increases were observed in all except glutamic acid, threonine, phenylalanine, and tyrosine concentrations (Wilcoxon signed rank test; p values given in table 3). The uniformity of the changes across infants was striking; in the case of most of the amino acids an increase was observed in every infant studied, notable exceptions being threonine, glutamic acid, phenylalanine, and tyrosine. The most appreciable increases were noted in ornithine, citrulline, cystine, methionine, glutamine, and alanine concentrations (fig 3).

Discussion

Dexamethasone treatment was associated with suppression of weight gain and striking increases in the plasma concentrations of most amino acids and urea. These changes could not be attributed to differences in nitrogen and energy intake between treatment periods. Our assumptions about the composition of human milk are unlikely to have influenced comparative nutrient intakes. This is firstly because the quantities employed were small and, secondly, because only within subject, between period comparisons were made. The small, statistically non-significant changes in the disposition of nutrient intake between parenteral and enteral routes are also unlikely to have been important, particularly as the protein:energy ratio was constrained during parenteral nutrition. Moreover, the pattern of hyperaminoacidaemia we describe differs from that previously observed by Räihä *et al* in dietary protein excess.[4–7] Concentrations of alanine, glycine, ornithine, lysine, histidine, serine, and threonine measured during dexamethasone treatment in our study were greater than those observed by Räihä *et al* in low birthweight infants fed unadjusted cows' milk protein at 4·5 g/kg/day. Conversely, the concentrations of leucine, isoleucine, valine, phenylalanine, tyrosine, citrulline, glutamate, and

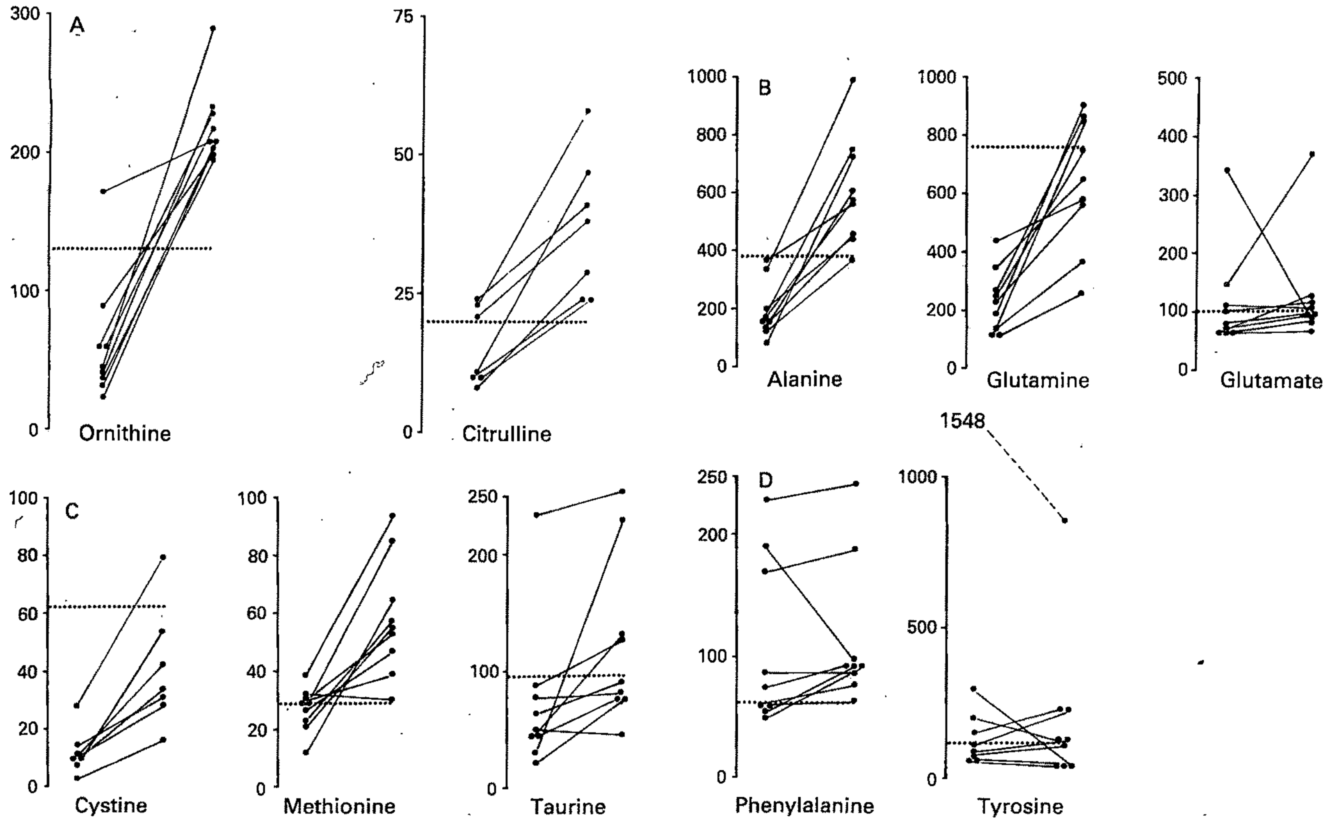

Figure 3 (A–D) Plasma amino acid concentrations in µmol/l. Values for samples taken before and after commencing dexamethasone are tied for individual infants. Dotted line indicates 90th centile value for ad libitum term breast fed infants.[18]

Table 3 *Concentrations of plasma amino acids before and after treatment*

	Median concentration (μmol/l) before treatment (range)	*Median concentration (μmol/l) after treatment (range)*	*p Value*	*Median concentration (μmol/l) for breast fed term infants*[18] *(10th, 90th centile)*
Ornithine	45 (24–171)	207 (195–287)	<0·001	84 (49, 116)
Citrulline	11 (8–24)	34 (16–58)	<0·001	13 (6, 20)
Cystine	11 (3–28)	34 (16–79)	<0·001	52 (34, 62)
Taurine	48 (22–236)	89 (46–256)	<0·001	50 (27, 96)
Methionine	29 (12–39)	55 (30–94)	<0·001	20 (13, 29)
Alanine	161 (83–362)	572 (371–992)	<0·001	235 (163, 387)
Asparagine	35 (8–96)	87 (58–120)	<0·001	53 (43, 87)
Glutamine	228 (114–440)	651 (258–902)	<0·001	610 (468, 755)
Glutamic acid	76 (64–341)	96 (68–368)	NS	56 (36, 98)
Glycine	295 (123–509)	558 (388–1007)	<0·001	183 (120, 228)
Serine	191 (86–316)	415 (213–599)	<0·001	109 (80, 143)
Threonine	176 (60–430)	260 (188–491)	NS	104 (76, 134)
Lysine	127 (43–278)	280 (194–410)	<0·001	148 (92, 210)
Histidine	74 (39–218)	136 (114–260)	<0·001	66 (44, 85)
Leucine	94 (67–164)	154 (103–170)	<0·002	103 (73, 160)
Valine	176 (120–274)	265 (143–391)	<0·001	153 (108, 184)
Isoleucine	40 (14–80)	59 (32–99)	<0·05	49 (32, 71)
Proline	150 (84–586)	281 (170–708)	<0·001	212 (162, 283)
Phenylalanine	75 (53–230)	94 (66–239)	NS	41 (23, 63)
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cystine which we measured were lower, and those of methionine, proline, glutamine, and taurine similar to those described by Räihä *et al.* The low cystine concentration measured in our study is particularly noteworthy and probably reflects the relatively high requirement for parenteral nutrition and low intake of human milk.

It seems unlikely that the plasma amino acid concentrations attained were intrinsically harmful as none approached levels characteristic of metabolic disease. Indeed, neonatal tyrosinaemia observed in one infant of 24 weeks' gestation improved after 48 hours of dexamethasone treatment, perhaps as a result of tyrosine aminotransferase induction.[8] The complexity of the metabolic response to steroid treatment makes it difficult, however, to be certain of the mechanisms underlying the changes that we have observed. The most important is likely to be a change in the balance between rate of protein synthesis and breakdown, but corticosteroid induced changes in active transport of amino acids across membranes could also affect cellular uptake. For example, corticosteroids reduce amino acid uptake by skeletal muscle and lymphoid tissue but increase uptake by hepatocytes.[9] The effects of corticosteroids on intracellular metabolism appear similarly complex—for example, hydrocortisone treatment both increased carbamoyl phosphate synthetase-I activity and decreased ornithine transcarbamoylase activity in fetal rat liver.[10] It is not clear to what extent the changes we observed in the urea cycle intermediates ornithine and citrulline were due to an overall increase in protein oxidation or to what extent any inhibition of ornithine transcarbamoylase might have been responsible.

Although the changes induced by glucocorticoids are often described as 'catabolic', protein turnover studies have suggested that nitrogen wasting results both from a decrease in protein synthesis and a rise in degradation rates,[11 12] though the latter may fall in some tissues.[12] Skeletal muscle has been considered to show the most appreciable effects. In the rat, those muscles with the highest proportion of fast fibres (for example, extensor digitorum longus) show the most noticeable atrophy and reduction in protein synthesis, whereas those with a greater proportion of slow fibres (for example, soleus) tend to be spared. The diaphragm, which contains a mixture of fast and slow fibres, appears to behave in an intermediate manner.[12 13] At present, there are no data on the effect of corticosteroids on diaphragmatic structure and function in the immature human infant.

The effect of corticosteroids on skeletal muscle has also been extensively studied in mature dogs. Muhlbacher *et al* showed a significant efflux of glutamine from skeletal muscle in animals given 0·44 mg/kg/day of dexamethasone.[14] However, the changes which they observed in plasma amino acid concentrations differ from those which we have noted in immature infants. Most notably, ornithine, glutamine, and cystine concentrations *fell* while alanine increased by a factor of only 1·5. In contrast, rats treated with 6 mg/kg/day of dexamethasone showed a rise in plasma glutamine concentration accompanied by efflux of glutamine and alanine from the lung.[15] This is of interest because the human and the rat, unlike the dog and other species studied, appear to release glutamine from the lung.[15] A recent observation that dexamethasone treatment appreciably suppresses lung growth and protein synthesis in the adolescent rat[16] raises the possibility that the increased plasma alanine and glutamine concentrations we describe here could be attributable as much to suppression of protein synthesis in the lung as in skeletal muscle. By analogy with the effects of dietary protein restriction in the rat this might be expected to increase lung compliance[17] and produce short term clinical improvement, but also to slow the rate of repair.

In summary, we observed striking increases in the plasma concentrations of most amino acids in immature infants treated with dexamethasone. These changes may reflect suppression of protein synthesis in both the lung and the respiratory musculature, but the relative contributions of effects of membrane transport and intermediary metabolism remain to be determined.

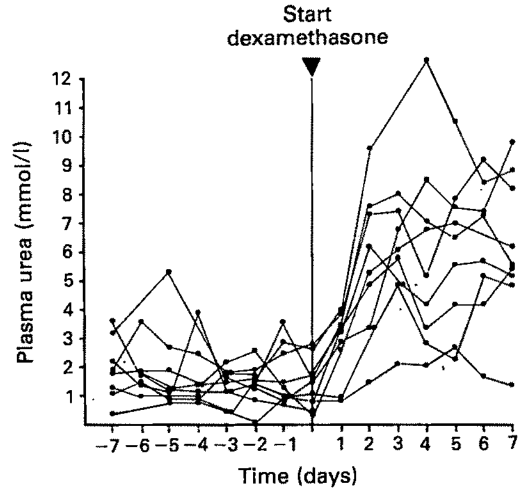

Figure 2 Plasma urea values (mmol/l) during the week before commencing dexamethasone and during the first week of treatment.

both the median plasma urea concentration and variability between individuals during treatment.

PLASMA AMINO ACID CONCENTRATIONS

Table 3 shows the median concentration (with range) for each amino acid before and after treatment. Significant increases were observed in all except glutamic acid, threonine, phenylalanine, and tyrosine concentrations (Wilcoxon signed rank test; p values given in table 3). The uniformity of the changes across infants was striking; in the case of most of the amino acids an increase was observed in every infant studied, notable exceptions being threonine, glutamic acid, phenylalanine, and tyrosine. The most appreciable increases were noted in ornithine, citrulline, cystine, methionine, glutamine, and alanine concentrations (fig 3).

Discussion

Dexamethasone treatment was associated with suppression of weight gain and striking increases in the plasma concentrations of most amino acids and urea. These changes could not be attributed to differences in nitrogen and energy intake between treatment periods. Our assumptions about the composition of human milk are unlikely to have influenced comparative nutrient intakes. This is firstly because the quantities employed were small and, secondly, because only within subject, between period comparisons were made. The small, statistically non-significant changes in the disposition of nutrient intake between parenteral and enteral routes are also unlikely to have been important, particularly as the protein:energy ratio was constrained during parenteral nutrition. Moreover, the pattern of hyperaminoacidaemia we describe differs from that previously observed by Räihä *et al* in dietary protein excess.[4–7] Concentrations of alanine, glycine, ornithine, lysine, histidine, serine, and threonine measured during dexamethasone treatment in our study were greater than those observed by Räihä *et al* in low birthweight infants fed unadjusted cows' milk protein at 4·5 g/kg/day. Conversely, the concentrations of leucine, isoleucine, valine, phenylalanine, tyrosine, citrulline, glutamate, and

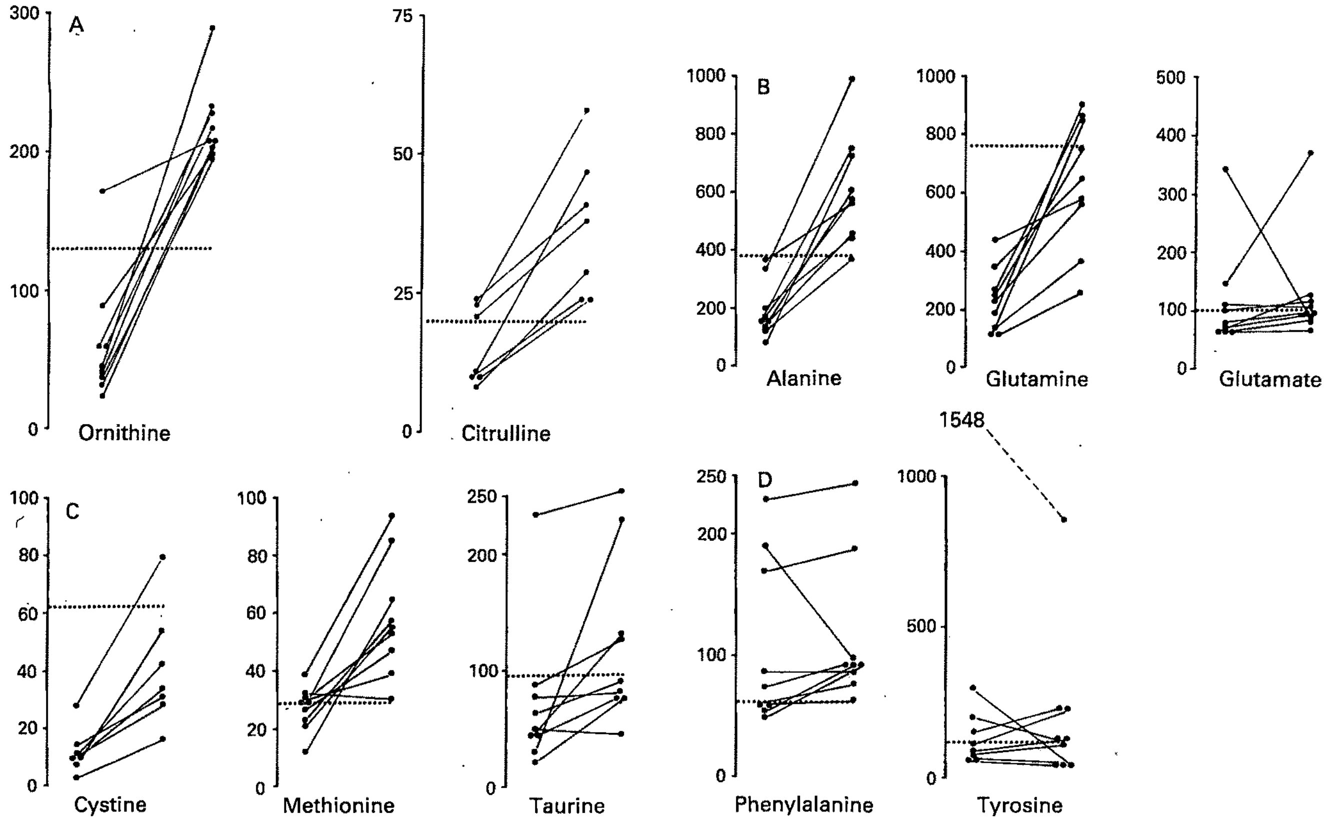

Figure 3 (A–D) Plasma amino acid concentrations in μmol/l. Values for samples taken before and after commencing dexamethasone are tied for individual infants. Dotted line indicates 90th centile value for ad libitum term breast fed infants.[18]

Table 3 Concentrations of plasma amino acids before and after treatment

	Median concentration (μmol/l) before treatment (range)	*Median concentration (μmol/l) after treatment (range)*	*p Value*	*Median concentration (μmol/l) for breast fed term infants*[18] *(10th, 90th centile)*
Ornithine	45 (24–171)	207 (195–287)	<0·001	84 (49, 116)
Citrulline	11 (8–24)	34 (16–58)	<0·001	13 (6, 20)
Cystine	11 (3–28)	34 (16–79)	<0·001	52 (34, 62)
Taurine	48 (22–236)	89 (46–256)	<0·001	50 (27, 96)
Methionine	29 (12–39)	55 (30–94)	<0·001	20 (13, 29)
Alanine	161 (83–362)	572 (371–992)	<0·001	235 (163, 387)
Asparagine	35 (8–96)	87 (58–120)	<0·001	53 (43, 87)
Glutamine	228 (114–440)	651 (258–902)	<0·001	610 (468, 755)
Glutamic acid	76 (64–341)	96 (68–368)	NS	56 (36, 98)
Glycine	295 (123–509)	558 (388–1007)	<0·001	183 (120, 228)
Serine	191 (86–316)	415 (213–599)	<0·001	109 (80, 143)
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In summary, we observed striking increases in the plasma concentrations of most amino acids in immature infants treated with dexamethasone. These changes may reflect suppression of protein synthesis in both the lung and the respiratory musculature, but the relative contributions of effects of membrane transport and intermediary metabolism remain to be determined.

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Dexamethasone treatment during ventilator dependency: possible life threatening gastrointestinal complications

Elizabeth A O'Neil, Walter J Chwals, Michael D O'Shea, Charles S Turner

Abstract

Corticosteroids in high doses have been used effectively to decrease the duration of ventilator dependency in very low birthweight infants at risk for chronic lung disease. Randomised prospective studies have shown benefit, with only minimal complications being reported. However, review of our experience over 2·5 years with high dose steroids in 80 premature neonates yielded three major complications: one case each of perforated duodenal ulcer, perforated gastric ulcer, and upper gastrointestinal haemorrhage. Two of the three patients died.

Thus the use of steroids in neonates may not be without risk, and significant complications can occur. When high dose corticosteroids are to be used in very low birthweight neonates, H_2 receptor antagonist treatment and gastric pH monitoring are recommended. The physician must remain alert to the possibilities of upper gastrointestinal bleeding and ulcer perforation in these patients.

High dose steroids have been used frequently in the management of ventilator dependent premature infants. Several studies have shown that such treatment accelerates weaning from assisted ventilation and improves pulmonary compliance, and the reported complication rates have been low.[1–5] Over a 2·5 year period, we have treated 80 ventilator dependent infants with high doses of dexamethasone. Among these infants three have had major complications associated with steroid usage: a perforated duodenal ulcer, a perforated gastric ulcer, and an upper gastrointestinal haemorrhage. Two infants died, resulting in a mortality of 66%. In contrast to the experience of others, then, our experience suggests that significant complications can occur when dexamethasone is used in infants at risk for bronchopulmonary dysplasia.

Dexamethasone is a synthetic steroid having a glucocorticoid effect about 30 times more potent than endogenous cortisol.[6] Most protocols start dexamethasone at an initial dose of 0·5 mg/kg/day given either enterally or parenterally.[1–5] The patient is weaned from the dexamethasone on all protocols, but the times and rates vary. At our institution we use the dexamethasone protocol described by Cummings *et al*: initial treatment with a dose of 0·5 mg/kg/day, which is decreased to 0·3 mg/kg/day after three days, and thereafter reduced by 10% every three days until 0·1 mg/kg/day is reached.[5] At that point, the drug is given every other day until day 42. The dosage is not changed in the presence of sepsis. Body weight, blood pressure, blood glucose values, and triglyceride concentrations are monitored.

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Case reports

CASE 1

A girl weighing 700 g born after 25 weeks' gestation was immediately intubated for respiratory distress. After 3·5 weeks of mechanical ventilation, high dose intravenous dexamethasone treatment (0·5 mg/kg/day) was begun. On the fourth day of steroid treatment at that dose she developed hypoxia, tachycardia, and abdominal distention; an abdominal radiograph showed free intraperitoneal air. Enteral feeding had not been initiated. At exploratory surgery, a perforated duodenal ulcer was found and repaired. Before H_2 receptor antagonist treatment was started, her gastric pH was 1·7 and her non-fasting serum gastrin concentration was 224 ng/l (normal range for non-fasting serum gastrin in infants: 100–225 ng/l[7]).

The postoperative course was otherwise uneventful. She was weaned from steroid treatment over several days and extubated on postoperative day 7.

CASE 2

A boy weighing 860 g born after 28 weeks' gestation was intubated immediately and remained ventilator dependent for three weeks. High dose intravenous dexamethasone (0·5 mg/kg/day) was begun, and 10 days later free intraperitoneal air was seen on a routine chest radiograph. The dexamethasone dose at this point was 0·2 mg/kg/day. At operation, a perforated ulcer was found on the lesser curvature of the stomach proximal to the pylorus. During repair of the ulcer the patient became hypotensive and died.

CASE 3

A boy weighing 900 g was born after 29 weeks' gestation. After 16 days of ventilator dependency, high dose intravenous dexamethasone (0·5 mg/kg/day) was begun. Two days later he developed copious bright red nasogastric drainage and guaiac positive stools. Despite aggressive treatment, including blood transfusions and an H_2 receptor antagonist, gastrointestinal haemorrhage persisted and he died five days after the start of steroid treatment. The dexamethasone dose at the time of death was 0·08 mg/kg/day. No postmortem examination was performed.

Discussion

All three patients from our series were low birthweight premature neonates. All developed severe clinical complications after a short course of high dose steroid treatment. A single perforated ulcer was found in two patients; the third patient had significant upper gastrointestinal haemorrhage. These findings agree with the observation of Grosfeld *et al* that acute peptic ulceration in infants tends to be solitary[8] and with the finding of Tolia and Dubois that peptic ulceration in neonates tends to present as free intraperitoneal air and severe clinical deterioration.[9]

The complications associated with high dose dexamethasone treatment reported from several prospective studies have been minimal, however. Harkavy *et al* reported hyperglycaemia as the only complication in a group of neonates treated with high dose dexamethasone for a minimum of two weeks.[2] Gladstone *et al*[1] and Kazzi *et al*[4] reported no complications in their high dose steroid treated neonates after five days and 17 days, respectively. Cummings *et al* noted no important gastrointestinal bleeding in their treatment group; however, the control group had a higher incidence of guaiac positive gastric aspirates.[5] Finally, Alkalay *et al* noted that four of 10 infants being given high dose steroids developed mild gastrointestinal haemorrhage, which responded to antacid treatment and/or cessation of enteral feedings.[3] Their steroid protocol was similar to that used at our institution.

Several cases of peptic ulceration and its complications had been reported before the high dose steroid protocol became popular. Grosfeld *et al* reported a 17 day old neonate who developed a perforated duodenal ulcer while being given steroids for idiopathic thrombocytopenic purpura.[8] That patient was also treated surgically for a bleeding duodenal ulcer during the same hospitalisation. Chhattriwalla *et al* reported two premature infants being given steroids for pulmonary deterioration who developed upper gastrointestinal haemorrhage.[10] In neither of these reports was the steroid dosage specified.

There is still controversy over the ulcerogenic potential of steroid treatment, and numerous papers support each side of the controversy. Conn and Blitzer reviewed prospective investigations from 1950 to 1975 and found no statistical difference in the incidence of peptic ulcers in patients treated with steroid versus those treated with placebo.[11] On the other hand, although acid hypersecretion is rarely observed with acute stress ulceration,[8 12] steroid treatment may result in decreased mucus secretion, and in the setting of a compromised mucosal barrier, even normal concentrations of acid might be sufficient to cause ulceration.

The common misconception that premature infants cannot make gastric acid[13 14] may lead physicians to believe that neonates are at lower risk for the gastrointestinal complications of steroid treatment and that prophylactic antacids are not indicated. It is noteworthy that the patient in case 1, a 3 week old premature neonate, was found to have a gastric pH of 1·7 after the diagnosis of a perforated ulcer. Therefore, we believe that prophylactic H_2 receptor antagonist treatment may be beneficial for neonates receiving high dose steroids who are not receiving gastric feeding. We do not recommend oral antacids, because clamping the nasogastric tube in the small neonate may predispose to aspiration. We also recommend that gastric pH be serially monitored in the neonate receiving steroids who is not receiving gastric feedings.

When steroid related complications such as bleeding or perforation do arise we recommend, in addition to appropriate surgical care, that steroid treatment be discontinued, while keeping in mind the possibility of the hypothalamic-pituitary-adrenal axis suppression. Our first patient was safely weaned from 0·5 mg/kg/day of intravenous dexamethasone over a four day period without adverse sequelae.

In summary, as the high dose steroid protocol is used more frequently for treating ventilator dependency in premature infants, the potential for severe complications and possible death must be kept in mind. Because a long term benefit of high dose dexamethasone has not been proved, we suggest, as have others, that further clinical trials be carried out to identify potential complications of high dose dexamethasone before its use becomes standard practice in ventilator dependent neonates at risk for chronic lung disease.

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Low dose intraventricular fibrinolytic treatment to prevent posthaemorrhagic hydrocephalus

A Whitelaw, R P A Rivers, L Creighton, P Gaffney

Abstract

Posthaemorrhagic ventricular dilatation (PHVD) is thought to be due to clots from intraventricular haemorrhage obstructing cerebrospinal fluid pathways involved in reabsorption. Over 60% of infants with progressive PHVD have gone on to require surgical shunt placement. Previous treatments all have major problems. The object of this pilot study was to achieve enough fibrinolysis to restore pathways of cerebrospinal fluid reabsorption and so avoid shunt surgery. Nine preterm infants with progressive PHVD were treated with intraventricular infusion of streptokinase for 12–72 hours. All the infants survived and surgical shunting was required in only one case. A 200% increase in fibrinolytic activity was demonstrated in both ventricular and spinal fluid during streptokinase treatment. There were no cases of infection. Minor rebleeding occurred in one case and was not a serious problem. This represents the first direct therapeutic approach to the pathology of PHVD.

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Posthaemorrhagic ventricular dilatation is one of the most serious complications of prematurity. It occurs after intraventricular haemorrhage and is assumed to be caused by small particles of blood clot obstructing the flow of cerebrospinal fluid through the ventricular system, basal cisterns, and arachnoid villi on the surface of the cerebral hemispheres. Subsequent chronic infiltration with collagen converts a potentially reversible hydrocephalus into a permanent one.[1]

Small sick infants are not suitable for shunt surgery because of high cerebrospinal fluid protein and poor pulmonary status and shunting later is associated with a high rate of blockage and infection.[2] Repeated tapping of spinal or ventricular cerebrospinal fluid can temporarily reduce pressure and control head enlargement but there is a 7% risk of meningitis with repeated taps.[3] Attempting to reduce cerebrospinal fluid production with acetazolamide produces metabolic acidosis in all infants and carbon dioxide retention in preterm infants with chronic lung disease.[4] Hence there is a great need for alternative approaches to treatment of posthaemorrhagic hydrocephalus.

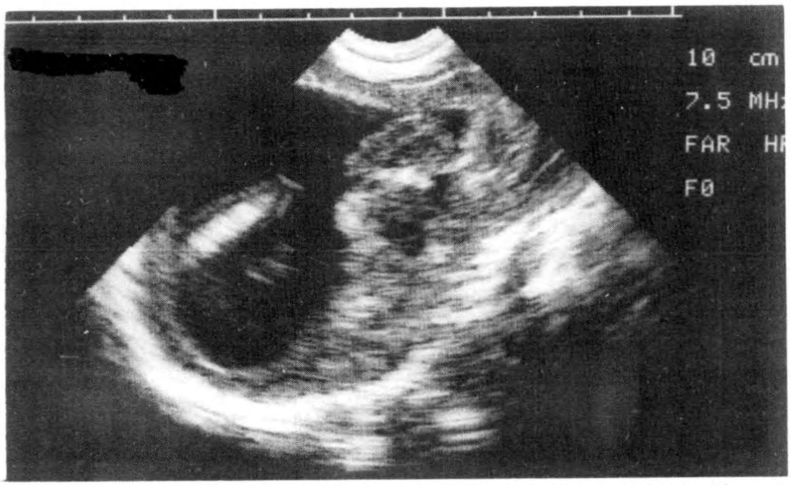
The use of urokinase for prevention of hydrocephalus after intraventricular haemorrhage was investigated in a controlled study in dogs by Pang *et al.*[5] They showed that 20 000 units of intraventricular urokinase every 12 hours significantly reduced hydrocephalus and cerebral damage after injection of blood into a lateral cerebral ventricle. Newman and Stewart described the use of intraventricular urokinase and streptokinase to activate plasminogen and so prevent hydrocephalus in 17 infants with meningitis.[6 7] They used up to 25 000 units of streptokinase per dose with no evidence of bleeding or inflammatory reaction. Todo *et al* described the intraventricular urokinase treatment of six adult patients with intraventricular haemorrhage.[8] Intraventricular urokinase was started as soon as one day after onset of symptoms at a dose of 10 000 units twice a day. They concluded that shunt requirement and neurological disability were reduced when compared with historical controls. No rebleeding due to urokinase treatment was seen. In the light of these therapeutic possibilities, we have carried out a pilot study to determine whether the fibrinolytic agent, streptokinase, can be used to prevent permanent hydrocephalus and shunt dependence after intraventricular haemorrhage in preterm infants.

Patients and methods

The data from Newman and Stewart on the elimination of streptokinase from the cerebrospinal fluid suggested that a continuous infusion into a cerebral ventricle would be necessary to obtain an effect over a prolonged period of time.[6] The table shows the characteristics of the nine infants who received a course of streptokinase. They ranged in gestational age from 25 to 31 weeks and in birth weight from 724 g to 1750 g. Intraventricular haemorrhage had been diagnosed by ultrasound in all cases within 96 hours of birth and the ventricular width of each lateral ventricle had subsequently enlarged to 4 mm over the 97th centile for postmenstrual age.[3] Streptokinase treatment was started at a postnatal age ranging from 8 days to 27 days. One other infant with massive intraventricular haemorrhage was initially considered suitable for streptokinase treatment because of ventricular enlargement. Soon after insertion of the ventricular catheter it was discovered that the infant had a capsular haematoma of the liver and the streptokinase infusion was aborted. A blood sample taken at the time showed no evidence of a systemic streptokinase effect.

The treatment regimen consisted of intraventricular infusion of 20 000–25 000 units of streptokinase/24 hours for 48 to 72 hours. The streptokinase (Streptase, Behringwerke or Kabikinase, Kabi) was made up in 0·9% sodium chloride or 5% dextrose solution and given at 0·5 ml/hour. The 20 gauge catheter (Ledercath, Vygon) was inserted through the lambdoid suture 1·5 cm lateral to the midline into the temporal horn of the larger of the lateral ventricles, using a needle and guidewire technique (figure). The catheter insertion was done under ultrasound imaging via the anterior fontanelle in three cases. After withdrawal of fluid to achieve a reduction in cerebrospinal fluid pressure, the continuous infusion of streptokinase was started. In infant 1 (table) a bolus of streptokinase (10 000 units) was given in 0·5 ml before the infusion.

A lumbar puncture was carried out during the streptokinase infusion, withdrawing 10 or more ml of cerebrospinal fluid to help the streptokinase to spread through the ventricular system to the subarachnoid space. Intraventricular vancomycin 1 mg was given at the start of the procedure and intravenous vancomycin was given for 72 hours as prophylaxis against infection. Twice daily ultrasound measurements were made of ventricular size and ventricular fluid was removed, if necessary, in order to maintain a low cerebrospinal fluid pressure (1–2 mm Hg) and so prevent any tendency for fluid to back-track around the catheter and escape under the transparent occlusion adhesive dressing. Two of the infants were treated at Hammersmith Hospital, London, two at Queen Charlotte's Hospital, London, two at Aker University Hospital, Oslo, two at Ullevål University Hospital, Oslo and one at St Mary's Hospital, London. The above procedure was approved by the Hammersmith and Queen Charlotte's research ethics committee and the research ethics committee of Oslo Regional Health Authority. Informed consent was given by all the parents.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Cranial ultrasound scan (right parasaggital view) on infant 8 showing the right ventricle (posterior is to the left of the picture) with the tip of the ventricular catheter entering the occipital horn from the lambdoid suture.

FIBRINOLYTIC ACTIVITY IN CEREBROSPINAL FLUID

The method was an adaption of that of Astrup and Mullertz.[9] Using an imidazole buffer (50 mM imidazole: 140 mM sodium chloride at pH 7·3), a bed of fibrin agarose was made with the following final concentrations: 2·5 mg/ml human fibrinogen (KabiVitrum grade L), 0·25 IU/ml human thrombin (MRC reagent 66/305) in low gelling temperature agarose (Sigma Chemical Co) in a glass dish. After setting, holes 4 mm in diameter were bored out of the plate and filled with samples of cerebrospinal fluid. The plate was then incubated in a moist atmosphere at 37°C for 18 hours after which the fibrinolytic activity was assessed by squaring the diameter of the clear lysis zones created by the samples. The larger the lysis zone, the greater the activity.

Fibrinolytic activity in blood was monitored by serial measurements of fibrinogen levels in all cases, D-dimer analysis in two cases and the euglobulin clot lysis time in one case.

Results

All the infants have survived and only one has gone on to develop progressive hydrocephalus requiring surgical shunting (table). Infants 3, 7, and 8 had technical problems necessitating catheter removal with consequent reduction in the total dose delivered. Infant 3 developed fresh intraventricular bleeding resulting in discontinuation of the streptokinase infusion. The liquid blood was aspirated from the ventricle and, after a blood transfusion, the infant's condition stabilised. This infant did not develop progressive hydrocephalus or parenchymal cystic cerebral lesions. Infant 7 received a course of acetazolamide in addition to the streptokinase infusion.

In infant 2, fibrinolytic activity (area on the plate in mm^2) was 480 in ventricular cerebrospinal fluid before streptokinase, 1820 in ventricular cerebrospinal fluid during streptokinase treatment, and 1550 in lumbar cerebrospinal fluid during streptokinase treatment. In no case was there any evidence of a streptokinase effect in the circulating blood as indicated by a decrease in plasma fibrinogen, increase in D-dimers, decreased euglobulin clot lysis time, or generalised bleeding tendency. No cases of cerebrospinal fluid or local infection occurred in connection with the streptokinase treatment.

Details of infants studied

Infant No	*Birth weight (g)*	*Gestational age (weeks)*	*Age at treatment (days)*	*Dose (units)*	*Shunt*	*Alive*	*Infection*	*Bleeding*
1	1393	30	11	70 000	No	Yes	No	No
2	1298	28	10	40 000	No	Yes	No	No
3	996	27	8	7 000	No	Yes	No	Yes
4	724	25	13	40 000	Yes	Yes	No	No
5	1016	26	8	40 000	No	Yes	No	No
6	900	26	22	40 000	No	Yes	No	No
7	1750	31	20	38 000	No	Yes	No	No
8	1180	27	22	13 000	No	Yes	No	No
9	1520	30	18	40 000	No	Yes	No	No

Discussion

The percutaneous placement of a ventricular catheter via the lambdoid suture allows simultaneous viewing of the procedure by ultrasound probe on the fontanelle. Despite the highly invasive nature of the technique it can be carried out with a no-touch sterile technique. Because of the risk of staphylococcal infection and its serious consequences, we chose to treat prophylactically with both local and systemic vancomycin. No infection occurred.

The low dose and local nature of the treatment would not be expected to give a systemic fibrinolytic effect with consumption of fibrinogen and none was found. The one case of intraventricular rebleeding was easily diagnosed and effectively treated without apparent complications. The demonstration of increased fibrinolytic activity in lumbar cerebrospinal fluid during streptokinase infusion is important as it is the subarachnoid cerebrospinal fluid which bathes the likely sites where small multiple clots obstruct reabsorption of cerebrospinal fluid when the hydrocephalus is communicating. All cases in this study had communicating hydrocephalus. The lumbar puncture during ventricular streptokinase infusion may be important to try and 'draw' the streptokinase down to the sites where it needs to be active. In addition, it serves to lower pressure if the intraventricular infusion of 12 ml per day has raised cerebrospinal fluid pressure. If necessary, normal ventricular pressure can be maintained by repeatedly withdrawing ventricular fluid.

We have shown that the techniques of streptokinase infusion can be carried out in preterm infants. On the basis of the multicentre ventriculomegaly trial, 62% (five or six infants out of nine reaching the criteria for inclusion) would have been expected to have reached surgical shunting.[3] Thus the finding of only one shunt being required in the nine cases is encouraging. Further studies are needed to address questions as to optimal dosage and duration of treatment as well as safety and effectiveness of this direct therapeutic approach to the prevention of progressive posthaemorrhagic hydrocephalus and permanent shunt dependence.

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Symmetrical thalamic lesions in infants

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Abstract

Clinical observations and findings on imaging are reported in six newborns with symmetrical thalamic lesions (STL). In three cases the diagnosis was confirmed by postmortem examination. Characteristic observations in this series and 17 previously reported cases include no evidence of perinatal asphyxia, high incidence of polyhydramnios, absent suck and swallow, absent primitive reflexes, appreciable spasticity at or within days of birth, lack of psychomotor development, and death within days or months. Characteristic pathological findings include loss of neurons, astrogliosis, and 'incrusted' neurons particularly in the thalamus. In two thirds of cases the basal ganglia and brain stem are involved as well. A hypoxic-ischaemic event occurring two to four weeks before birth is most likely responsible for STL. Bilateral thalamic calcification can often, but not always, be demonstrated in the newborn period by computed tomography and/or cranial ultrasound. The presence of these calcifications and the observation of spasticity at birth imply that the responsible insult occurred at least two to four weeks earlier. The small number of published cases with STL suggest that it may be easily missed.

The first cases of symmetrical thalamic lesions in infants (STL) were reported in 1962 by Rosales and Riggs.[1] In the subsequent 28 years only 14 additional cases have been reported.[2–9] Six cases of STL were seen at our hospital between 1982 and 1991. We would like to draw attention to this condition with particular emphasis on neonatal clinical presentation and findings on imaging. In this context we have preferred the term thalamic lesions, instead of the initial designation of thalamic degeneration used by Rosales and Riggs, to avoid the assumption of a progressive system degeneration.

Case reports

Relevant data of the published cases and our own observations are summarised in the table. The diagnosis was confirmed by postmortem examination in three of our cases; in the other three the diagnosis was based on typical clinical presentation and neuroradiological findings.

CASE 1

The mother was a 29 year old primigravida. The girl was born at 35 weeks' gestation by emergency caesarean section due to breech presentation and maternal haemorrhage. The pregnancy had been uncomplicated except for an upper respiratory tract infection with fever in the last four weeks. The amniotic fluid was stained with meconium. The umbilical cord arterial pH was 7·29 and venous pH was 7·31. Apgar scores were 5, 9, and 9 at 1, 5, and 10 minutes. The infant was intubated due to increasing respiratory distress. The chest radiograph showed a totally opaque left lung, presumably due to atelectasis.

Clinical findings

The birth weight was 1820 g (10th centile) and the head circumference was 30·5 cm (10th–50th centile). The infant made no spontaneous movements, there was pronounced spasticity with leg abduction, exaggerated tendon reflexes, and absent suck and swallow (fig 1). Upon establishing the diagnosis of bilateral thalamic lesions it was decided, in view of the poor prognosis, to withdraw aggressive support. She died some hours later at 4 days of age.

Additional investigations

Cranial ultrasound on the second day of life showed mild irregular periventricular hyperechogenicity and narrow lateral ventricles. Magnetic resonance imaging on the fourth day of life gave normal results. An electroencephalogram (EEG) at 3 days was within normal limits. A metabolic screen (amino acids and organic acids) and TORCH serology (toxoplasma, rubella, cytomegalovirus, and herpes virus) were negative.

Summary of relevant data in all published cases of STL including the present series

	Previously published cases (n=17)[*]	*Present series* (n=6)
Mean duration of pregnancy (weeks)	37	38·5
Range	32–42	35–40·5
Polyhydramnios	5/10	3/6
Apgar score at 1 minute $\leqslant 4$	2/10	1/6
Apgar score at 5 minutes $\leqslant 6$	6/9	3/6
No spontaneous motor activity	6/9	4/6
Spasticity:		
From birth	5/16	3/6
Within days of birth	6/16	3/6
Absent primitive reflexes	8/8	5/6
Absent swallow	15/15	5/6
Neonatal convulsions	8/14	1/6
Postmortem examination:		
Thalamic lesions	14/14	3/3
Basal ganglia affected	4/14	2/3
Brain stem involved	9/14	1/3

[*] Information not complete for all cases.

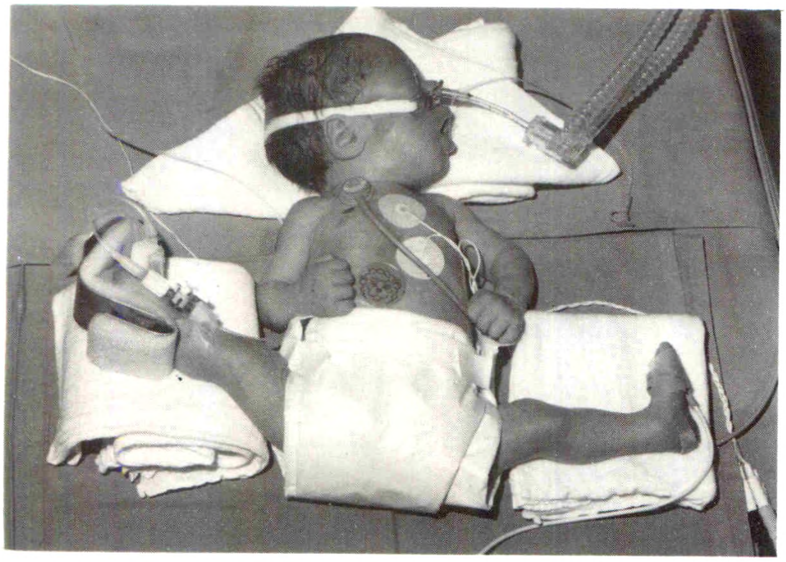

Figure 1 Case 1 at 3 days showing appreciable spasticity with abduction of lower limbs.

Findings on postmortem examination

Severe gliosis with mineralised neurons and neuronal loss in both thalami, hypothalamus, corpus geniculatum mediale, dorsal pons, and medulla oblongata were found. There was mild oedema and interstitial emphysema of the lungs.

CASE 2

The mother was 28 years old and gravida two, para two. The pregnancy had been complicated by polyhydramnios (time of onset not documented). At 35 weeks' gestation an abnormal external fetal heart rate trace was noted but a repeat on the next day was normal. An amnioscopy was normal. The girl was born by spontaneous vaginal delivery at 37 weeks' gestation. The amniotic fluid was stained with meconium. The umbilical cord arterial pH was 7·26 and venous pH was 7·48. Apgar scores were 6, 8 and 9, at 1, 5, and 10 minutes.

Clinical findings

The birth weight was 3220 g (90th centile) and the head circumference was 35·2 cm (greater than 90th centile). Decreased spontaneous activity, hypotonia with hyperreflexia, and absent suck and swallow were noted. Gavage feeding was necessary. She had symmetrical but reduced facial movements, incomplete closure of the eyes, and an absent corneal reflex. She made no psychomotor progress and died unexpectedly after a respiratory arrest at 6 weeks of age.

Additional investigations

Cranial ultrasound on the second day of life demonstrated increased echogenicity in the region of the thalamus that was more distinct on the left side. Computed tomography on the sixth day showed diffuse subcortical hypodensities and irregular density of the thalami (fig 2). An EEG on the third day showed multifocal discharges but no seizures were observed. A metabolic screen (amino acids and organic acids) and TORCH serology were negative.

Findings on postmortem examination

Mineralised neuronal necrosis bilaterally in the lateral thalamus, diffuse gliosis of the cortex, and severe aspiration pneumonia were found.

CASE 3

The mother was 41 years old and gravida three, para one. She had had two previous spontaneous first trimester abortions. Because of maternal age, the boy was born by elective caesarean section at 39 weeks' gestation after an uncomplicated pregnancy. The Apgar scores were 9, 9, and 9 at 1, 5, and 10 minutes. At 24 hours of life severe hypoglycaemia occurred and was treated with glucose infusion.

Clinical findings

The birth weight was 3430 g (50th–90th centile) and the head circumference was 36 cm (50th–90th centile). At birth the infant was apathetic, spontaneous movements were clearly diminished, and muscle tone was generally increased. He was a poor feeder, there was repeated vomiting, and difficulty maintaining body temperature. He did not fix with his eyes. There was pendular horizontal and vertical nystagmus. The pupils did not react to light. The optic discs appeared hypoplastic. Laboratory examinations showed hypothalamic panhypopituitarism. (Thyroid stimulating hormone 4·6 mU/l (normal range 1–3·7), thyroxine 60 nmol/l (65–145), cortisol 28 nmol/l (200–500), luteinising hormone 36 μg/l (low), follicle

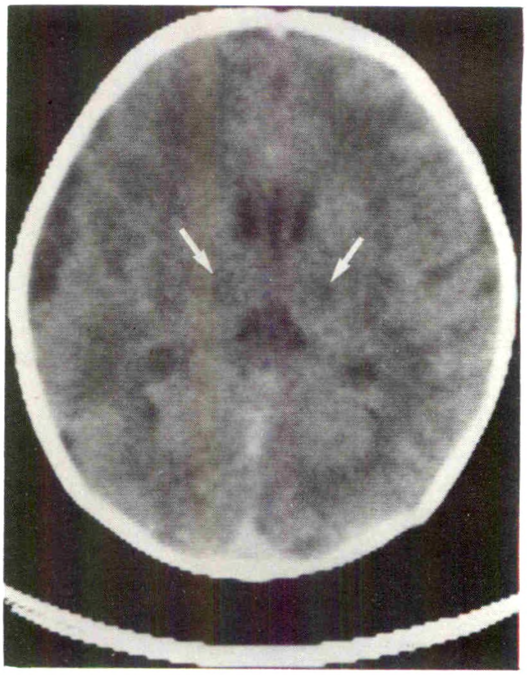

Figure 2 Computed tomogram of case 2 at 6 days showing diffuse irregular hypodensities of the white matter, thalami hypodense (arrows). Thalamic lesions were confirmed at postmortem examination.

stimulating hormone 7 μg/l (low), and basal prolactin 2073 mU/l (≤500).) After hormonal substitution with thyroxine (at 4 weeks), corticosteroids (at 4 weeks), and vasopressin (at 7 weeks) the infant's general condition improved: his vomiting stopped and he was able to drink. At 8 weeks of age, during a discharge examination, he appeared well and his muscle tone and reflexes were normal. He had persistent vertical and horizontal nystagmus and absent pupillary reaction to light. At 8·5 months he died unexpectedly at home.

Additional investigations

Cranial ultrasound on the sixth day showed mild dilatations of the lateral ventricles. At 4 weeks a distinct hyperechogenic lesion was seen in the thalamus bilaterally (fig 3). In retrospect this was also visible on a prior, technically suboptimal study. At 8 weeks there was mild increase in size of the lesions with increasing width of the lateral ventricles. Computed tomography on the 26th day confirmed the ultrasound findings (fig 4).

Findings at postmortem examination

There were symmetric calcifications in the lateral thalamus, globus pallidus, and capsula interna with hypoplastic corticospinal tracts, with incrusted neurons, axonal swelling, and neuroaxonal dystrophy. A von Kossa stain was positive. Diffuse gliosis and decreased myelination of the white matter was found as well as septo-optic dysplasia with hypoplastic nerves and tracts. Additional findings included hypoplasia of the nerve fibre and ganglion layer in the retina, cataract, hypoplasia of anterior and posterior pituitary lobes, appreciable hypoplasia of both adrenal glands and testes, and micropenis.

CASE 4

The mother was 31 years old and gravida four, para four. She had Hodgkin's disease and had been treated with chemotherapy and radiotherapy five years before this pregnancy. She had three healthy children. The pregnancy was complicated by polyhydramnios. Amnioscopy and external heart rate monitoring five days before birth were normal. The girl was born by uneventful spontaneous vaginal delivery at 39 weeks' gestation. Seven litres of clear amniotic fluid were noted. Apgar scores were 5, 5, and 7 at 1, 5, and 10 minutes. The infant required oxygen by mask and some hours later had to be intubated because of respiratory acidosis (pH 7·18, carbon dioxide tension 8·3 kPa).

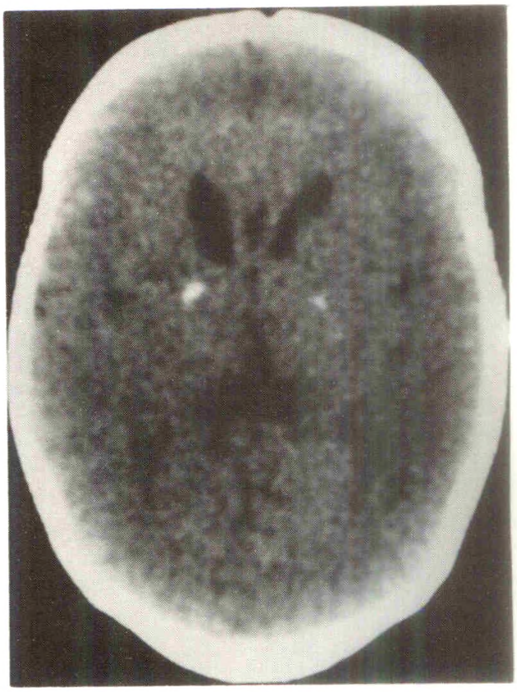

Figure 4 Case 3: Computed tomogram at 26 days with bilateral hyperdensities in the thalamic region.

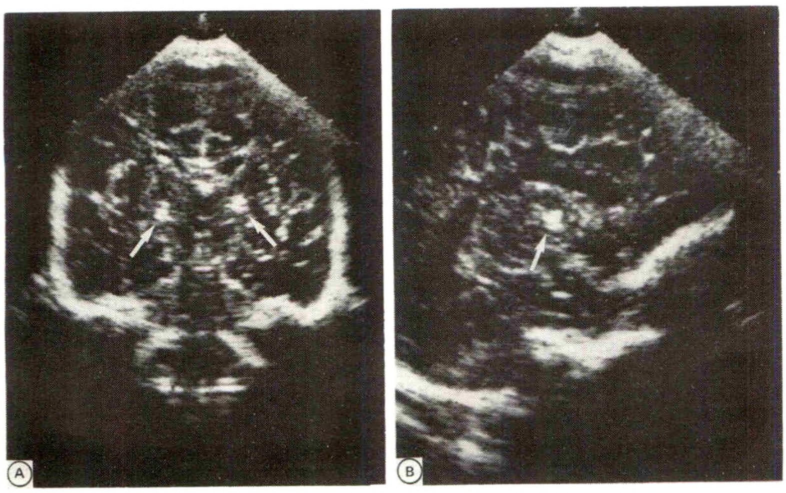

Figure 3 Case 3: (A) coronal and (B) sagittal sonograms at 4 weeks of age with a distinct hyperechogenic lesion of the thalamic region bilaterally (arrows).

Clinical findings

The birth weight was 3240 g (50th–90th centile) and the head circumference was 32 cm (slightly less than 3rd centile). She showed no spontaneous activity, suck, or swallow. Appreciable spasticity with bilateral subluxation of the hips was observed in the delivery room. Deep tendon reflexes were brisk with bilateral ankle clonus. A diagnosis of STL was very likely in our view, therefore on the third day the infant was extubated and died 12 hours later.

Additional investigations

Cranial ultrasound on the first day showed a large third ventricle. Permission for postmortem examination was refused.

CASE 5

The mother was a 22 year old primigravida. After an uncomplicated pregnancy the girl was born at 40 weeks' gestation by a caesarean section because of abnormal external heart rate monitoring and failure to progress. Umbilical cord arterial pH was 7·29. Apgar scores were 1, 6, and 9 at 1, 5, and 10 minutes. The infant briefly required bag and mask ventilation in the delivery room.

Clinical findings

The infant weighed 3280 g (50th centile) and her head circumference was 37 cm (greater than 90th centile). At birth she was hypotonic but after several days the upper limbs became increasingly spastic. Primitive reflexes were absent. Because of absent suck and swallow gavage feeding was necessary. Nursing care was complicated by hypersalivation. Severe apnoea prompted intubation and mechanical ventilation from day 7 to 10. Mild seizures occurred at 5 days and were successfully treated with phenobarbitone. At 7 months the clinical findings were nearly identical: pronounced spasticity with increased tendon reflexes and absent suck and swallow. Gavage feeding was continued. There was no motor development. She died age 8·5 months at home.

Additional investigations

Cranial ultrasound on the fifth day of life showed hyperechogenic areas in the region of the lateral thalamus. Computed tomography on the ninth day showed a distinct bilateral hyperdensity in the lateral thalamic/putaminal area (fig 5). Magnetic resonance imaging was tried on two occasions but was not possible because of considerable breathing difficulties after head positioning; imaging with intubation and anaesthesia was not felt justified. Permission for postmortem examination was refused.

CASE 6

The mother was 31 years old and gravida five, para four. At 35 weeks' gestation she noted absent fetal movements and feared that the fetus was dead. Auscultation of fetal heart rate was normal; fetal heart rate monitoring and sonography were not done. An ultrasound investigation at 38 weeks showed polyhydramnios, which had not been present at 33 weeks. The boy was born by uncomplicated spontaneous delivery at 38 weeks' gestation. Amniotic fluid was clear. Umbilical cord arterial pH was 7·24 and venous pH was 7·30. Apgar scores were 5, 6, and 8 at 1, 5, and 10 minutes.

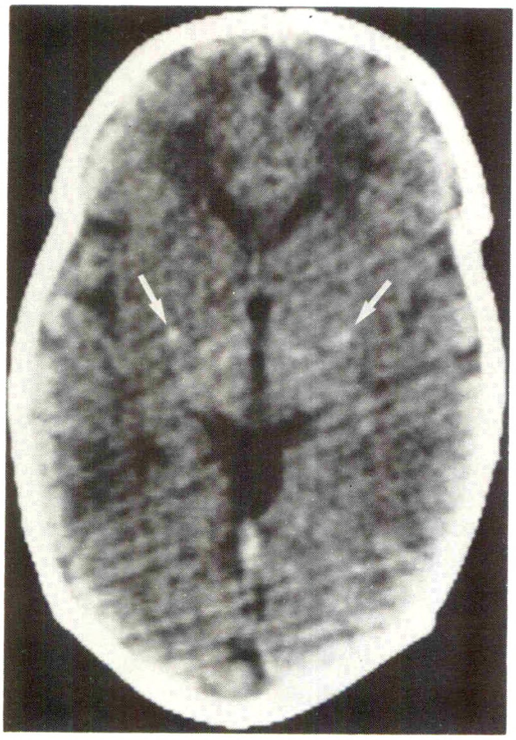

Figure 5 Case 5: Computed tomogram at 9 days showing small hyperdensities in the putaminal region.

Clinical findings

The birth weight was 3490 g (50th–90th centile) and the head circumference was 34 cm (10th–50th centile). In the delivery room the neurological examination was striking: the infant was hypotonic and could not suck or swallow. A few hours later deep tendon reflexes were exaggerated, primitive reflexes were absent, and motor activity was diminished. Twenty two hours after birth spasticity of the legs was noted. Because of repetitive apnoea and carbon dioxide retention the child was intubated and transferred to our hospital. In our view the history and findings were typical for STL. On the sixth day of life the child was extubated; he died 30 minutes later.

Additional investigations

Cranial ultrasound on the sixth day of life was normal. Computed tomography on the fifth day showed diffuse subcortical hypodensities that were similar to case 2 (and had been proved at postmortem examination). An EEG on day 4 showed immature cerebral background activity with multifocal paroxysmal discharges without obvious seizures. A metabolic screen (amino acids, lactate, and pyruvate) was normal. Permission for postmortem examination was refused.

Discussion

STL appears to have a characteristic constellation of findings (table). Polyhydramnios is common and is likely to be caused by impaired intrauterine swallowing of amniotic fluid. This supports the idea of a prenatal origin for STL, which is also suggested by the presence of spasticity at or within days of birth. In almost all cases absence of suck, swallow, and primitive reflexes were observed. In our series neonatal convulsions were seen in only one patient (case 5). Other cranial nerve signs (pupillary abnormalities, disturbed ocular motility, and facial weakness) were occasionally noted in our patients (cases 2 and 3). Only in case 5 was there evidence of perinatal hypoxia; the Apgar scores and umbilical cord pH in all other cases were normal.

The prognosis of STL seems very poor. The reported patients have died within days to weeks or have survived, severely damaged, for only a few months. In view of this experience artificial ventilation was withdrawn in our cases 1, 4, and 6.

If STL is considered on clinical grounds we recommend a neuroradiological work up repeated as necessary. Ultrasonography is a useful tool in this work up: in our series thalamic hyperechogenicity was seen in three out of five cases.[10 11] Computed tomography was performed in four patients. There was evidence of thalamic hyperdensity in two infants but not in the other two (one proved at postmortem examination). Our experience with magnetic resonance imaging is limited but it gave normal results in case 1 (STL proved at postmortem examination). These observations confirm the findings of Roland *et al*[8] and DiMario and Clancy[9] that neuroimaging may be normal at an initial stage and has to be repeated subsequently in surviving patients who have a clinical diagnosis of STL.

Neuropathological examination commonly demonstrates a thalamic lesion with additional and variable involvement of basal ganglia and brain stem. The typical histological findings consist of neuronal loss, astrogliosis, and 'incrusted' neurons. It is of interest that the astrogliosis often has a different topographic distribution and is not limited to the thalamus. The clinical signs are not easily explained by the neuropathological lesions. Case 3 is unusual in that he had in addition to STL, findings compatible with septo-optic dysplasia and panhypopituitarism.

Because the time interval required before appreciable tissue calcification becomes visible is two or more weeks,[12] it is likely that an event leading to STL occurs at least two weeks before birth. It is of great interest that in this time period significant events have been noted in many cases: abnormal cardiotocography 11 days before birth in case 2 and sudden loss of fetal movements three weeks before birth in case 6. Also reported are maternal trauma with subsequent labour four weeks before birth,[6] salicylate intoxication three weeks before birth[2] and reduced fetal movements in last few weeks of pregnancy.[7] Therefore an acute hypoxic-ischaemic event occurring two to four weeks before birth is considered a likely possible explanation for STL. Myers[13] and Ranck *et al*[14] found similar histological changes in the thalamus and brain stem after a single episode of total anoxia in monkey fetuses.

So far published cases of STL have been sporadic with the exception of two siblings reported by Abuelo *et al*.[4] The empiric recurrence risk for further similarly affected children appears to be very low.

STL of prenatal onset has to be separated from postnatal spontaneous intrathalamic haemorrhage (which has a comparatively favourable outcome[15]) as well as from thalamic haemorrhages observed after severe perinatal asphyxia.[16 17]

As we have been able to collect six cases within eight years, and the total number of previously reported cases is only 17, we feel that STL may be more common than previously thought. The diagnosis may be missed if the clinical signs are not recognised. Normal neuroimaging in the newborn period does not exclude the diagnosis and repeated investigations may be needed.

We are grateful to Dr E Martin, Dr D Mieth, and Dr U Hunziker for additional information.

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Evaluation of techniques for delivery of steroids to lungs of neonates using a rabbit model

Christopher O'Callaghan, John Hardy, Julie Stammers, Terence J Stephenson, David Hull

Abstract

Little is known about delivery of aerosolised steroids to neonatal patients undergoing assisted positive pressure ventilation and after extubation. A rabbit model has been established to investigate factors influencing drug delivery.

Beclomethasone dipropionate, in a metered dose inhaler, was radiolabelled with technetium 99m. The mass median aerodynamic diameter of the aerosol was 3·3 (2·0) µm and the impactor measurements confirmed that the technetium distribution corresponded with that of the drug particles. The metered dose inhaler was actuated into a collapsible spacer that was used to ventilate and deliver aerosol to anaesthetised rabbits by a tracheostomy. From each actuation of the drug 2·9 (0·4)% of the aerosol deposited in the trachea and main bronchi and 1·2 (0·4)% in the lung. When the drug was delivered by a spacer device, with facemask attachment, to rabbits breathing freely through a tracheostomy, aerosol deposition increased to 4·4 (2·1)% in the trachea and main bronchi and 1·9 (0·9)% in the lung lobes. The maximum change in systolic blood pressure after administration of aerosol by the collapsible spacer was a decrease of 13%.

The methods described may prove useful for the delivery of inhaled steroids to neonatal patients likely to develop bronchopulmonary dysplasia.

Oral steroids in the form of dexamethasone have been used with some success in the treatment of bronchopulmonary dysplasia.[1 2] However, dexamethasone given over long periods may be associated with significant side effects such as prolonged suppression of the hypothalamic-pituitary-adrenal axis.[3]

Since their introduction, inhaled steroid aerosols have become the mainstay of treatment of asthmatic patients with moderate to severe symptoms, reducing the need for large systemic doses. The considerably smaller dose used for inhalation treatment is associated with few side effects. It is postulated that low doses of inhaled steroid started early in the management of very low birthweight infants requiring ventilation may reduce the severity of bronchopulmonary dysplasia by reducing inflammation and subsequent tissue damage.

One of the conclusions from a recent workshop on aerosol treatment in the newborn was that technical problems of delivering suspended particles by aerosol need urgent solution in view of clinical demand for topical steroid treatment by aerosol in newborns.[4] The aim of this study was to use a rabbit model to assess methods of delivery of aerosolised steroids to the airways. The results of these experiments may lead to improvements in aerosol delivery to neonatal patients.

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Methods

RADIOLABELLING OF BECLOMETHASONE DIPROPIONATE

Technetium 99m was used to radiolabel beclomethasone dipropionate aerosol (Becotide, Allen and Hanburys). Sodium pertechnetate was extracted from saline into butanone and added to an empty beclomethasone dipropionate aerosol can. The solution was evaporated to dryness and the can cooled in liquid nitrogen. A beclomethasone dipropionate metered dose aerosol (50 µg/actuation;200 actuations/can) was also cooled in liquid nitrogen, opened, and the contents decanted into the can containing technetium 99m. A valve system was then crimped on to the can. At the time of dosing each can delivered approximately 1 MBq technetium 99m/actuation.

PARTICLE SIZING

A multistage liquid impinger, as described by May in 1966,[5] and modified by Bell *et al*,[6] was used to measure the aerodynamic particle size distribution of the aerosol cloud. The impinger had been calibrated by sampling an aerosol of dibutyl phthalate droplets previously sized using a reference impacter (Cassella Impacter, CF, Cassella). The radiolabelled beclomethasone dipropionate preparation was fired into a Volumatic spacer device (Glaxo) with the valve closed. The spacer was plugged into the mouthpiece of the multistage liquid impinger through which air was drawn at 60 l/minute. This was repeated 25 times. The impinger was imaged using a gamma camera and the distribution of radioactivity quantified. The study was repeated under identical conditions using non-labelled beclomethasone dipropionate metered dose inhalers. The impinger samples containing the drug were collected in methanol/water (50/50) and assayed against a range of known concentration beclomethasone dipropionate standards using high pressure liquid chromatography.

On the basis of the data acquired for the multistage liquid impinger, together with the 50% cut off diameter for each stage of the device, a plot of aerodynamic diameter against cumulative percentage of particles below each size was constructed. The graph was used to calculate the mass median aerodynamic diameter (MMAD:the droplet diameter at which half the aerosol mass is contained in smaller droplets and half in larger droplets) and the geometric standard deviation (GSD:the ratio of the 84·1% diameter to the MMAD 50% diameter). The GSD is a measure of the width of the distribution of droplet diameter.

RABBIT PREPARATION

Eight New Zealand/California rabbits were studied. A 24 gauge catheter was inserted into a marginal ear vein and anaesthesia induced with 5 ml/kg of 20% (w/v) ethyl carbamate (urethane, Sigma Chemical Co). A tracheostomy was performed and a size 3·0 endotracheal tube inserted. An 18 gauge catheter was inserted into the left carotid artery for blood pressure measurement and sampling for blood gas analysis. The catheter was kept patent by an infusion of 0·9% (w/v) saline at 1 ml/hour. Further doses of 20% (w/v) urethane were given as required up to a maximum dose of 8 ml/kg.

TIDAL VOLUME MEASUREMENT

The tidal volume of each rabbit was measured via the tracheostomy tubes connected to a 200 litre rigid container by two tubes with internal diameters of 18 mm as described by Stokes *et al.*[7] A flow of 4 l/minute was conducted to the mask by a battery driven fan which was situated in one of the connecting tubes. This method eliminated any dead space in the system. A carbon dioxide absorber was included in the circuit. The pressure changes (<1 cm H_2O/10 ml) occurring within the container as a result of the rabbit's breathing were measured by a pressure transducer (Furness Controls, FC 40) and relayed through a custom built calibration unit to a chart recorder. Calibration was carried out by injecting and withdrawing air using a 20 ml syringe.

ADMINISTRATION OF RADIOLABELLED AEROSOL TO RABBITS

(a) Via collapsible spacer device

A Laerdal resuscitation bag (Laerdal Ltd) was modified to act as a collapsible spacer. An opening was made in the base of the bag to allow access for the mouthpiece of the metered dose inhaler. The top end was fitted onto the tracheostomy tube with the rabbit lying on its back. The aerosol was then actuated into the device and immediately removed. The operators gloved hand (to protect from radioactivity on the skin) was placed over the opening at the base of the bag to act as a seal. The spacer device was then squeezed from the sides at a rate of 40/minute for 30 seconds. The pressure applied was determined by observation of adequate chest wall movement. The pressure release valve of the Laerdal resuscitation bag was left in the system for safety.

Continuous blood pressure measurements were made in the four rabbits during the procedure to determine if inflation of the rabbit chest in this manor caused hypotension due to decreased venous return to the heart.

(b) Via spacer device with facemask attachment

A Nebuhaler device (Astra) with facemask attachment[8] was used to deliver the aerosol by a 3·0 mm tracheostomy tube to anaesthetised freely breathing rabbits lying on their backs. Firm card was fitted tightly around the tracheostomy tube and the mask placed onto this to create a seal to mimic placement over an infant's face. The spacer device was held in a vertical position above the tracheostomy and radiolabelled beclomethasone dipropionate actuated into the device. The rabbit was allowed to breathe through the mask for 30 seconds. This was repeated at 30 second intervals for a total of eight actuations. Tidal volume was measured before and after administration. Samples for blood gas analysis were also taken before drug delivery. This study was carried out in four rabbits.

MEASUREMENT OF AEROSOL DEPOSITION

Rabbits were killed immediately after the aerosol administration. The lungs and trachea were dissected out and separated into individual lobes and placed in a small plastic bag. The amount of radioactivity in each lobe and in the trahea and bronchi were assayed in a large volume sample counter. Individual lobes were weighed and cut into two parts, central and peripheral. These sections were reweighed and the radioactivity measured. The amount of radioactivity from a single actuation of aerosol was collected into a plastic container at the time of each experiment and used to calibrate the equipment. The counting geometry was the same during the assay of both calibration standards and the lung specimens.

Table 1 Details of rabbit weight, tidal volume, respiratory rate, and blood gases

Rabbit No	*Weight (kg)*	*Tidal volume (ml)*	*Respiratory rate/minute**	*pH*	*Arterial carbon dioxide tension (kPa)*	*Arterial oxygen tension (kPa)*
1	3·1	NR	(40)	7·35	5·9	10·3
2	3·3	NR	(40)	7·32	5·8	10·9
3	3·0	NR	(40)	7·37	7·0	11·2
4	2·8	NR	(40)	7·43	4·4	13·0
5	2·6	11	78	7·41	5·3	11·1
6	2·9	8	65	7.4	5·2	10·2
7	3·4	7	60	7·46	5·2	10·5
8	3·1	7	72	7·48	5·5	10·6

*Respiratory rate of rabbits 1–4 represents rate/minute at which ventilated by collapsible spacer device.

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Results

The weight, respiratory rate, and arterial pH and carbon dioxide and oxygen tensions at the time of drug administration are recorded in table 1. Tidal volumes measured in the four rabbits given beclomethasone diproprionate by the spacer device with facemask attachment are also shown in table 1.

The percentage of beclomethasone dipropionate retained in the rabbit lung and major airways when administered by the collapsible spacer and Nebuhaler device are listed in tables 2 and 3. For each dose of beclomethasone dipropionate 2·9 (0·4)% of the aerosol deposited in the trachea and main bronchi and 1·2 (0·4)% in the lung when given by the collapsible spacer. For each dose of beclomethasone dipropionate 4·4 (2·1)% of the aerosol deposited in the trachea and main bronchi and 1·9 (0·9)% of the aerosol in the lung when given via the Nebuhaler with facemask attachment.

Deposition with in the lung lobes was calculated as the amount of aerosol per gram of tissue. Tables 4 and 5 show deposition of areosol (proportion of total lung deposition) in the individual lung lobes expressed as a percentage of total deposition in the lungs. The right lung received more aerosol (69%) than the left lung (31%) when administered by the collapsible spacer and when given via the Nebuhaler with facemask attachment (right 64%, left 36%). More aerosol was deposited in the upper lobes (right anterior azygous, right anterior, and left anterior, 61%) than the lower lobes (right posterior, right posterior azygous, and left posterior lobe, 39%) when administered by the collapsible spacer or by the Nebuhaler with facemask attachment, 58% and 42%, respectively. When individual lobes were divided into peripheral and central portions 54 (3)% of the radiolabel deposited in the lung lobes was contained in the proximal lung tissue compared with 46 (3)% in the peripheral tissue.

The maximum change in systolic blood pressure during and after ventilation with the collapsible spacer device was 13% and the mean (SD) systolic blood pressure 106 (12) mm Hg.

The MMAD (GSD) of the aerosol when determined from the technetium imaging data was 2·6 (2·1) µm and when determined by

Table 2 Proportion of beclomethasone dipropionate deposited in the rabbit lung when administered by metered dose inhaler by a collapsible spacer device

	Proportion of dose (%) in rabbit No				Mean (SD)
	1	2	3	4	
Total aerosol in the trachea, main bronchi, and lungs	4·5	3·3	3·7	4·9	4·1 (0·7)
Aerosol deposited in the trachea and main bronchi	3·0	2·3	2·8	3·3	2·9 (0·4)
Aerosol deposited in lung	1·5	1·0	0·9	1·6	1·2 (0·4)

Table 3 Proportion of beclomethasone dipropionate deposited in the rabbit lung when administered by metered dose inhaler by a Nebuhaler with facemask

	Proportion of dose (%) in rabbit No				Mean (SD)
	1	2	3	4	
Total in the trachea, main bronchi, and lungs	5·9	2·9	8·4	8·0	8·3 (2·5)
Aerosol deposited in the trachea and main bronchi	5·2	1·3	5·9	5·4	4·4 (2·1)
Aerosol deposited in lungs	0·7	1·6	2·5	2·6	1·9 (0·9)

Table 4 Proportion of beclomethasone dipropionate aerosol given by collapsible spacer deposited in individual lung lobes

	Proportion of lung dose in each lobe (%) in rabbit No				Mean (SD)
	1	2	3	4	
Right anterior azygous lobe	24	20	33	25	25 (5)
Right anterior lobe	17	11	17	17	16 (3)
Right posterior lobe	9	12	16	15	13 (3)
Right posterior azygous lobe	23	11	11	17	15 (6)
Left anterior lobe	19	30	14	16	20 (7)
Left posterior lobe	9	16	10	10	11 (3)

Table 5 Proportion of beclomethasone dipropionate aerosol given by nebuhaler with facemask deposited in individual lung lobes

	Rabbit No				Mean (SD)
	5	6	7	8	
Right anterior azygous lobe	35	17	17	24	23 (9)
Right anterior lobe	13	17	10	15	14 (3)
Right posterior lobe	10	15	20	13	14 (4)
Right posterior azygous lobe	14	18	6	15	13 (5)
Left anterior lobe	16	20	29	20	21 (5)
Left posterior lobe	12	15	19	15	15 (3)

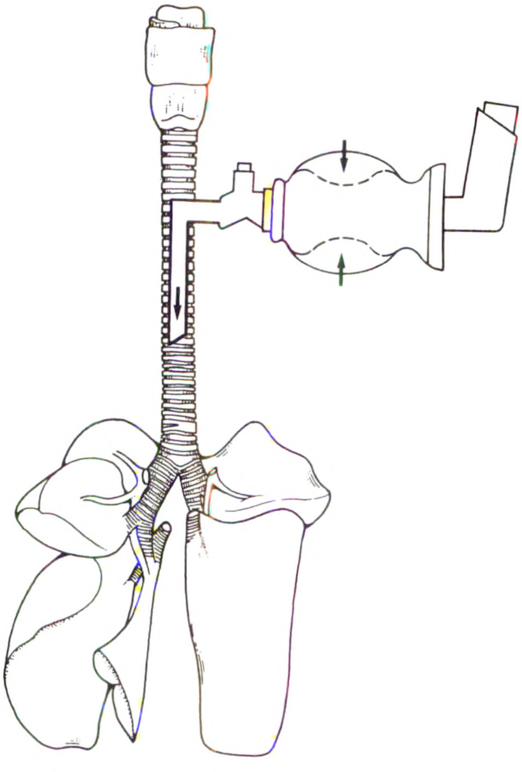

Figure 1 Administration of beclomethasone dipropionate, by a tracheostomy, to the lungs of an anaesthetised rabbit using the collapsible spacer device.

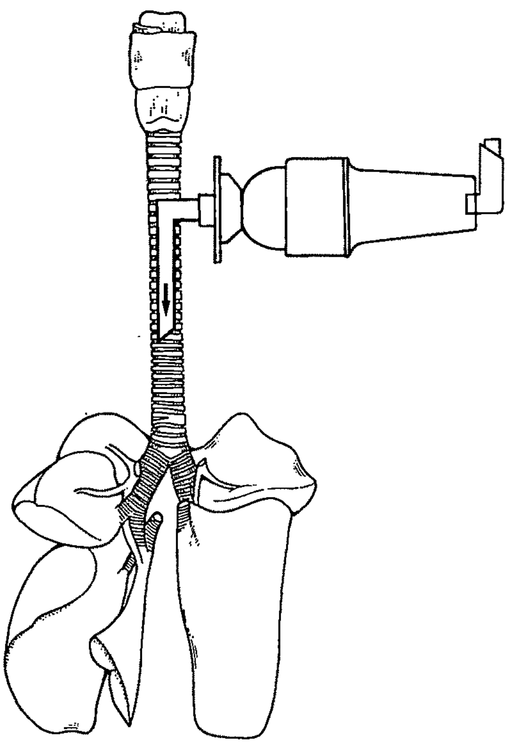

Figure 2 Administration of beclomethasone dipropionate from a spacer device with facemask attachment, by a tracheostomy, to the lungs of an anaesthetised rabbit.

assay of drug deposited with in the impinger, 3·3 (2·0) μm.

The method described provides satisfactory radiolabelling of beclomethasone dipropionate aerosol particles for administration from a metered dose inhaler. The particle size distribution calculated from drug assay and technetium label were similar, thus deposition of radiolabel in rabbits could be equated with drug deposition.

Discussion

The results from this pilot study are encouraging especially compared with deposition of therapeutic aerosols from metered dose inhalers in adults. Assuming a 70 kg adult has a good inhaler technique and achieves 10% lung deposition of actuated aerosol, the dose received from a 50 μg actuation is 0·07 μg/kg. When delivered to the rabbit by the collapsible spacer (0·13 μg/kg) or via the Nebuhaler with facemask (0·32 μg/kg) a considerably greater amount of beclomethasone dipropionate deposited in the rabbit lungs/kg body weight. Flavin *et al* achieved a lung deposition of only 0·19% in ventilated rabbits using a traditional nebuliser.[9] This improved to 1·96% when the drug was delivered by a nebuliser producing submicronic particles. Using a nebulised cloud with a mass median diameter of 1·3 μm, Cameron *et al*, using standard ventilator settings, achieved lung deposition of 2·8% of the aerosol released.[10] Wattenburg *et al* estimated that <1% of a nebulised test dose of sodium cromoglycate deposited in the lungs of their ventilated babies with bronchopulmonary dysplasia.[11]

Steroids used for nebulisation, however, are in a suspension rather than a solution and would not be released from a nebuliser generating submicronic particles. Poor clinical response seen after nebulisation of beclomethasone dipropionate suspension in asthmatic children may be explained by the low amount of steroid that is contained in particles likely to reach the airways.[12] A suspension of budesonide, suitable for nebulisation, has recently become available at a concentration 10 times that of the beclomethasone dipropionate suspension. In a ventilated lung model deposition of drug ranged from 0·06% to 2·7% depending on the nebuliser used.[13]

Greater deposition was seen in the upper lobes of the rabbits, which is similar to findings in other animal studies. This preferential deposition has been shown to be independent of body position.[14] Compared with instillation of drug into the lungs, however, delivery by aerosol results in a much more homogeneous deposition.[15] It was encouraging that over 40% of the drug depositing in a lung lobe reaches the outer half. A recent study of ventilated adult patients showed poor lung delivery after nebulisation (1·2% of the initial dose), but much better delivery (5·6% of initial dose) when the drug was given from a metered dose inhaler via a spacer chamber contained within the ventilator circuit.[16] Because neonates have much smaller endotracheal tubes the percentage of the initial total dose entering the lungs may be considerably less. The patient does not have to be disconnected from the ventilator circuit, however, which may be advantageous. In practice a neonatal patient receiving steroid aerosol by the collapsible spacer would have to be disconnected only twice a day. This should prove acceptable as ventilated babies are hand ventilated during suction of the endotracheal tube without apparent deleterious effect.

Once the neonatal patient is extubated, inhaled steroids may be continued using a spacer device with facemask attachment. Studies are required to determine the upper airway deposition of steroid in neonatal patients. The dose of steroid reaching the airways of neonatal patients may be considerably lower than seen in the present study if there is enhanced upper airway deposition. A pilot study involving the treatment of chronically wheezing infants with a steroid aerosol given by a spacer device with facemask attachment showed a very encouraging improvement in symptoms.[17] Asthmatic children aged 1–3 years have also shown improvement in symptoms in response to steroids delivered in this way.[18]

The adult rabbit as a model has limitations, as the lungs are usually normal and the pattern of airway branching differs from that of human airways. The model, however, provides a simple in vivo method of comparing aerosol deposition of various aerosols from different devices. This is preferable to studying radiolabelled aerosol deposition in large numbers of neonatal patients.

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Delivery of therapeutic aerosols to intubated babies

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Abstract

Delivery of drug aerosols to the lungs of ventilated neonates by metered dose inhaler and spacer (Aerochamber) and ultrasonic nebuliser (Pentasonic) was assessed using sodium cromoglycate.

The mean proportion of a known intratracheal dose of sodium cromoglycate excreted in the urine of four intubated infants was 37·5%. After assuming that 38% of the sodium cromoglycate aerosol reaching the neonatal lung will be excreted in the urine, three puffs (15 mg) delivered by metered dose inhaler and spacer resulted in a pulmonary dose of 258 μg (1·7%, n=7). A dose of 20 mg (4 ml) sodium cromoglycate ultrasonically nebulised over five minutes into the inspiratory limb of a standard ventilator circuit produced a pulmonary dose of 257 μg (1·3%, n=7).

Of two in vitro lung models assessed, a combination of filter and neonatal test lung was superior to a multistage impactor in estimating the in vivo pulmonary sodium cromoglycate dose delivered by metered dose inhaler and spacer (243 μg *v* 1740 μg).

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Therapeutic aerosols are often used in intubated neonates despite a paucity of information on the pulmonary dose or the most efficient delivery system. A number of devices are available for the production of therapeutic aerosols.

Jet nebulisation is widely used and bronchodilators administered by this method have been shown to improve lung function in intubated infants with bronchopulmonary dysplasia.[1] There are, however, problems with jet nebulisation including gas cooling,[2] reduction in humidity,[3] and a requirement for an auxiliary high pressure gas supply. It is also very inefficient, with 0·2% of the drug dose in the nebuliser reservoir reaching the neonatal lung.[4]

Table 1 Subject details

Subject No	*Gestation (weeks)*	*Weight (g)*	*Diagnosis*	*Sodium cromoglycate delivery method*
1	35	2100	Myopathy	IT+Pentasonic
2	35	4000	Persistent fetal circulation	IT+Pentasonic
3	41	4200	Myopathy	IT+Pentasonic
4	31	1700	RDS	IT+Pentasonic+Aerochamber
5	24	800	RDS	Pentasonic+Aerochamber
6	30	1400	RDS	Aerochamber
7	38	3500	Gastroschisis	Aerochamber
8	26	1000	RDS	Aerochamber
9	25	1100	RDS	Aerochamber
10	27	500	RDS	Aerochamber
11	30	1400	Apnoea	Pentasonic
12	38	4700	RDS (diabetic mother)	Pentasonic
13	36	1400	Congenital abnormalities	IT
14	26	1000	RDS	IT

RDS=respiratory distress syndrome; IT=intratracheal sodium cromoglycate dose.

Ultrasonic nebulisation and metered dose aerosol delivered by spacer are alternative delivery methods which have little effect on ventilator gas humidity or temperature. Neither has been assessed in intubated neonates.

The Pentasonic ultrasonic nebuliser (DeVilbiss) nebulises drugs using 2·25 MHz pizoelectric crystal. It weights 160 g and is portable. The Aerochamber with 15 mm connection (Trudell Medical) is a modification of an infant spacer device accepting standard metered dose inhalers (MDI) and is designed to be inserted into the inspiratory limb of an adult ventilator circuit. This 11×4·1 cm spacer has an approximate volume of 145 ml and allows aerosol to be generated within the centre of the ventilator gas flow. Both the Pentasonic and Aerochamber can be used in a neonatal ventilator circuit after minimal adaptation.

This study aimed to assess the efficiency of aerosol delivery to intubated infants lungs by using sodium cromoglycate as a marker of drug delivery. Sodium cromoglycate (Intal, Fisons plc) is non-toxic and is excreted unchanged in the bile and urine.[5] We first estimated the fraction of a known intratracheal dose of sodium cromoglycate excreted in the urine of ventilated neonates over 24 hours. By combining this information with 24 hour urinary sodium cromoglycate excretion after an ultrasonic or MDI dose, the total dose deposited in the lung was estimated. Pulmonary sodium cromoglycate deposition by MDI in vivo was then compared with that estimated in vitro by either a test lung with filter or a multistage impactor.

Methods

IN VIVO ASSESSMENT

Infants studied were receiving intermittent positive pressure ventilation via a pressure limited, time cycled ventilator (Sechrist) for a range of conditions. These included respiratory distress syndrome (n=8), myopathy (n=2), persistent fetal circulation (n=1), surgery (n=1), and multiple congenital abnormalities (n=1) (table 1). All infants were intubated by a shouldered endotracheal tube (Portex) and had blood urea and creatinine concentrations within the normal range.

This study was approved by the ethics committee of the Royal Postgraduate Medical School. Infants were studied after written parental consent.

Intratracheal dose

Isotonic sodium cromoglycate (1400 μg, 0·2 ml) was instilled through a size 5 French gauge suction catheter wedged in the right main bronchus of intubated neonates. Urine was collected over a 24 hour period and assayed for sodium cromoglycate by radioimmunoassay.[6] If leakage from the collecting bag occurred, the 24 hour collection was discarded. Sodium cromoglycate removed from the lung by suction was measured in the total pool of endotracheal aspirates collected over 24 hours after instillation. The actual intratracheal dose available to the infant was the difference between the intratracheal dose delivered and the amount removed by endotracheal suction. The proportion of the intratracheal dose excreted in the urine over a 24 hour period was then calculated.

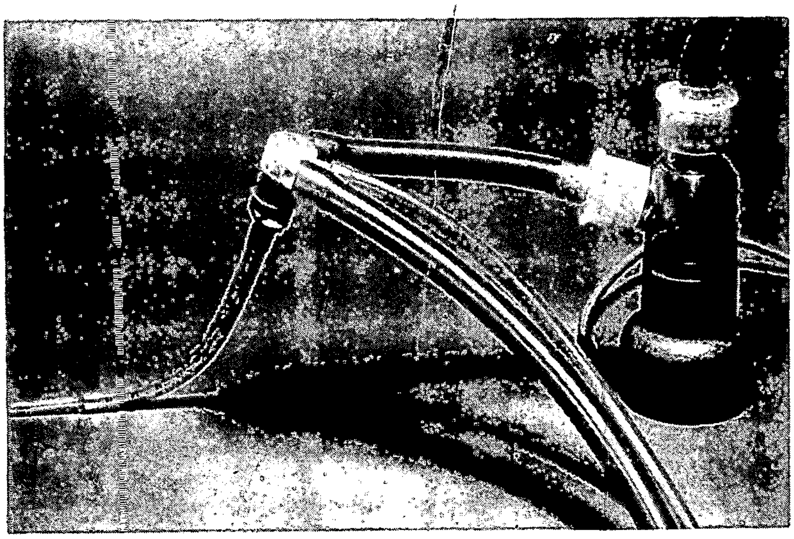

Figure 1 Pentasonic nebuliser inserted into the inspiratory limb of a ventilator circuit.

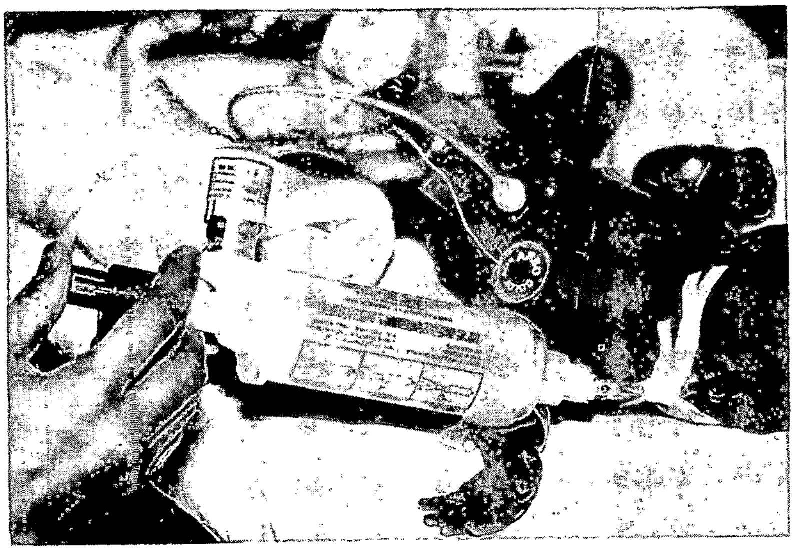

Figure 2 Ventilation through an Aerochamber spacer.

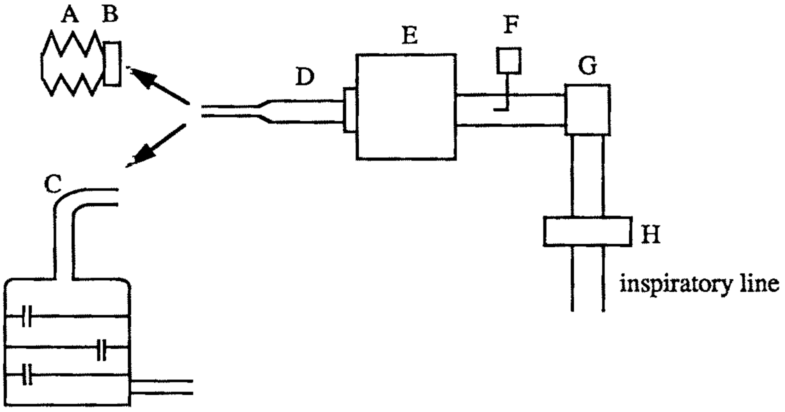

Figure 3 In vitro models of pulmonary sodium cromoglycate deposition by metered dose inhaler and spacer. A=test lung, B=filter, C=multistage impactor, D=3·5 mm endotracheal tube, E=Aerochamber, F=sodium cromoglycate metered dose inhaler, G=thumb occlusion valve, H=pressure release valve.

The urinary elimination half life of sodium cromoglycate was calculated from a plot of the midtime point for each urine collection (min) against the log excretion rate (μg/min).[7]

Assessment of nebuliser and MDI

The Pentasonic ultrasonic nebuliser was inserted directly into the inspiratory limb of the constant flow ventilator circuit, 10 cm from the right angled endotracheal tube connector (fig 1). Before insertion the one way inspiratory valve was removed from the nebuliser chamber. Humidified inspiratory gas entered the nebuliser through the upper part of the nebuliser and exited through a side port. The chamber was loaded with 20 mg sodium cromoglycate dissolved in 4 ml of normal saline and the nebuliser run for five minutes. The 24 hour urinary excretion of sodium cromoglycate was measured by radioimmunoassay on a single pooled sample.

The Aerochamber was inserted directly onto the endotracheal tube after disconnection from the ventilator circuit. Infants were then ventilated by a thumb occluded 'Nottingham puffer' set at a flow of 8 l/min and an appropriate blow off pressure and inserted into the end of the spacer (fig 2).

Each infant received three puffs of 5 mg sodium cromoglycate via MDI. The MDI was actuated at end expiration and each dose was separated by five manual breaths. After removing the spacer, infants were reconnected to the ventilator circuit and 24 hour pooled urinary sodium cromoglycate excretion measured by radioimmunoassay.

IN VITRO MODEL

Aerochamber assessment

The neonatal lung was modelled by a test lung (Draeger) inserted onto a 3·5 mm shouldered endotracheal tube. MDI aerosol passing through the endotracheal tube was collected by a 0·25 μm filter (Aerosol Medical) inserted between the tube tip and test lung (fig 3). The dose of sodium cromoglycate and method of administration were similar to that used in vivo. Inspiratory pressure was set at 20 cm H_2O giving a tidal volume to the test lung of 15 ml. After three MDI doses (15 mg), sodium cromoglycate was eluted from the filter with 20 ml water and measured by radioimmunoassay.

Particle size

The mass median aerodynamic diameter (MMAD) of particles generated by the ultrasonic nebuliser was measured by laser diffraction. Ultrasonic aerosol was generated within a continuous 8 l/min airflow which passed through 10 cm of ventilator tubing and 3·5 mm Portex endotracheal tube. Particle size was measured by a laser particle sizer (2600 Malvern Instruments) 2 cm from the endotracheal tube tip.

The MMAD of particles generated by MDI was measured by multistage impactor. Aerosol generated by MDI was carried through the Aerochamber and endotracheal tube by a gas flow of 8 l/min. This was then sucked into a multistage impactor operating at 60 l/min and separated into three size fractions (fig 3). Sodium cromoglycate deposited in each fraction after 20 doses (100 mg) was assayed by a spectrophotometer that had been previously calibrated using sodium cromoglycate solutions of known concentrations. The total dose deposited within the multistage impactor and MMAD of the aerosol was calculated from the amount eluted from each size fraction. At the end of the impactor experiment, sodium cromoglycate deposited in the endotracheal tube and Aerochamber was also eluted and assayed.

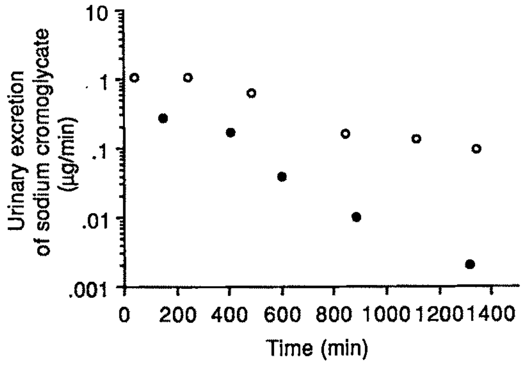

Figure 4 Urinary excretion of sodium cromoglycate from subjects 13 and 14.

Table 2 In vivo urinary excretion and estimated pulmonary deposition after sodium cromoglycate delivered by Aerochamber and metered dose inhaler

Subject No	*24 Hour urinary excretion of sodium cromoglycate* (µg)*	*Estimated pulmonary dose sodium cromoglycate† (µg)*
4	69	181
5	68	179
6	109	287
7	118	310
8	104	273
9	143	376
10	75	197
Mean (SEM)	98 (11)	258 (28)

*After 3×5 mg doses of sodium cromoglycate.
†Assuming urinary excretion 38% of pulmonary dose.

Results

IN VIVO

Four infants (subjects 1–4, table 1) had tracheal aspirates saved after a 1400 µg intratracheal dose enabling an estimation of the actual intratracheal dose available for systemic absorption. Mean urinary excretion as a percentage of the estimated intratracheal dose was 37·5% (range 22·3–59·7%). In two infants (subjects 13 and 14, table 1) several timed urine samples after the intratracheal dose were available, although their endotracheal aspirates were not saved. Their urinary excretion half lives were 100 and 310 minutes (fig 4).

Seven infants received a dose of sodium cromoglycate via the MDI and seven via the ultrasonic nebuliser. Mean (SEM) 24 hour urinary sodium cromoglycate excretion after a 15 mg dose via Aerochamber and MDI was 98 (11) µg (table 2). Mean 24 hour urinary sodium cromoglycate excretion after five minutes of ultrasonic nebulisation with a nebuliser fill of 20 mg was 98 (18) µg (table 3). Endotracheal suction was not performed until at least four hours after aerosolised sodium cromoglycate. However, endotracheal aspirates were not saved for radioimmunoassay.

Assuming that 38% of an inhaled dose of sodium cromoglycate is excreted in the urine, the Aerochamber and MDI delivered 258 (28) µg to the lung (1·7% of the 15 mg aerosolised dose). The Pentasonic delivered 257 (47) µg (1·3% of the initial 20 mg nebuliser fill).

IN VITRO

Mean deposition of sodium cromoglycate onto a filter situated between the endotracheal tube and test lung after 3×5 mg puffs delivered by MDI with Aerochamber was 243 µg (n=3). Total deposition within the multistage impactor after 20 puffs into the Aerochamber was 11·6 mg or 1740 µg per three MDI puffs (table 4). Of the total dose aerosolised by the MDI, 81·4% was deposited within the spacer and 7·8% in the endotracheal tube.

Table 3 In vivo urinary excretion and estimated pulmonary deposition after ultrasonic nebulisation of a sodium cromoglycate solution for 5 minutes

Subject No	*Ventilator gas flow (l/min)*	*Ventilator rate (per min)*	*Inspiratory time (sec)*	*24 Hour urinary excretion sodium cromoglycate* (µg)*	*Estimated pulmonary dose sodium cromoglycate† (µg)*
1	8	30	0·5	104	274
2	8	30	0·5	50	132
3	8	30	0·5	170	447
4	8	30	0·5	138	363
5	12	75	0·4	47	123
11	8	20	0·3	63	158
12	8	30	0·7	115	303
Mean (SEM)				98 (18)	257 (47)

*Nebuliser fill of 20 mg sodium cromoglycate in 4 ml.
†Assuming urinary excretion 38% of pulmonary dose.

Table 4 Comparison of in vitro and in vivo aerosol delivery of sodium cromoglycate

	Initial nebuliser fill or dose generated by MDI (mg)	*Mean pulmonary dose in vitro or in vivo (μg) (% of initial dose)*	*MMAD (μm)*
Aerochamber+MDI in vitro; multistage impactor*	15	1740 (11·6)	9·0
Aerochamber+MDI in vitro; filter+test lung (n=3)	15	243 (1·62)	
Aerochamber+MDI in vivo (n=7)	15	258† (1·72)	
Pentasonic in vivo (n=7)	20	257† (1·28)	3·4‡

*Calculated from 100 mg initial dose.
†Estimated assuming urinary excretion 38% of pulmonary dose.
‡Measured in vitro using Malvern laser particle sizer.

The MMAD of particles generated by MDI, after passing through the Aerochamber and endotracheal tube, was 9·0 μm. MMAD of ultrasonically nebulised sodium cromoglycate after passing through an endotracheal tube was 2·8 μm (table 4).

Discussion

The Pentasonic nebuliser and Aerochamber with MDI delivered a detectable dose of sodium cromoglycate to ventilated neonates. A significant proportion of the sodium cromoglycate aerosol generated by both delivery systems was in droplets small enough to penetrate the distal airways. The pulmonary dose of sodium cromoglycate aerosolised by MDI, estimated from the urinary excretion of a known intratracheal dose, was similar to that deposited on a filter model using a neonatal test lung. However, the dose deposited in a multistage impactor significantly overestimated the in vivo dose.

Estimation of the pulmonary dose in vivo depends on the proportion excreted in the urine. Most published data is from adult subjects. Sodium cromoglycate is not metabolised in the lung or liver and is excreted unchanged in the bile and urine.[5] Some 70–90% of a 1 mg dose of sodium cromoglycate instilled into the adult lung by fibreoptic bronchoscope will be absorbed into the circulation and of this, 33–46% is excreted in the urine.[8] [9] The plasma half life of either a bronchoscopically instilled or inhaled dose is 64–165 minutes after an initial rapid half life of 1·9 minutes, with lung absorption being the rate limiting step.[8] The pulmonary dose calculated from urinary excretion is similar to that obtained using plasma data.[10] The wide variability in the fraction of intratracheal sodium cromoglycate excreted in the urine of ventilated neonates in this study is not surprising. Pulmonary atelectasis, mucus, and epithelial damage may have significantly altered sodium cromoglycate bioavailability between infants. When combined with the clinical problems of collecting endotracheal aspirates and urine samples, the fractional urinary excretion must be regarded as only a rough approximation. However, if the urinary excretion half life is less than seven hours, a collection period of 24 hours should have contained most of the dose excreted in the urine.

Combined in vitro and in vivo assessment of aerosolised drug delivery in ventilated neonates has previously been reported. Watterberg *et al*, using a multistage impinger model, detected 19% of the sodium cromoglycate dose placed in the reservoir of a jet nebuliser emerging from an endotracheal tube. However, when the same nebuliser and loading dose (20 mg) were used in vivo, less than 0·1% (20 μg) was excreted in the urine of intubated infants.[4] A similar overestimate of the in vivo pulmonary dose was obtained by the multistage impactor in our study and may result from incomplete modelling of aerosol behaviour. In a conventional pressure limited, time cycled ventilator, inspiration is a result of the build up of pressure within the circuit from obstructing gas exit while fresh gas in-flow continues. The requirement for a continuous gas flow during the rest of the cycle, means that a significant proportion of a constantly nebulised drug will be unavailable to the infant. If all the flow through the circuit is directed into a multistage impactor, drug wasted in the expiratory phase in vivo will be collected. There is a similar reason for the overestimation by multistage impactor of the dose delivered by Aerochamber with MDI. Here, the source of error is that the multistage impactor cannot model inspiratory and expiratory flow as aerosol needs to be continuously drawn through the impactor system. The combination of filter and neonatal test lung does model inspiration and expiration and the agreement between the in vivo pulmonary dose (258 μg) and sodium cromoglycate deposited on the filter (243 μg) after a 15 mg MDI dose reflects this improved modelling.

The filter model also has the advantage that, where aerosol is generated within the continuous gas flow, wastage of drug during expiration is modelled. Filter/test lung models seem to predict accurately jet nebulised aerosol delivery into neonatal ventilator circuits in vivo. Using aminophylline as a drug marker the Ultravent jet nebuliser delivers 0·22% of the reservoir dose to a test lung.[11] A figure of 0·2% has been reported after jet nebulisation in vivo.[4] Despite the errors in estimating the pulmonary dose of sodium cromoglycate aerosol, urinary excretion of sodium cromoglycate by the infants in this study reflects the absolute minimum amount of drug delivered to the lung. About 0·7% of the MDI dose and 0·5% of the ultrasonically nebulised dose was excreted in the urine over 24 hours. Although we did not measure it, the deposition of aerosol into the lungs by ultrasonic nebuliser is likely to be dependent on the pattern of mechanical ventilation, as it is for a jet nebuliser inserted into a ventilator circuit.[12]

The Pentasonic has not previously been assessed in vivo although the Aerochamber has been used to deliver bronchodilators to intubated adults receiving volume cycled ventilation. An Aerochamber and MDI inserted into the inspiratory limb of a ventilator circuit will deliver 5·7% of the original dose to the adult lung.[13] In adult ventilator circuits, there is no continuous flow and most of the aerosolised drug is delivered to the patient's endotracheal tube. By placing the Aerochamber directly onto the neonate's endotracheal tube the problem of continuous flow is overcome and delivery partially mimics that of the volume cycled ventilator. It may also be possible to enhance ultrasonic drug deposition by placing the nebuliser directly onto the endotracheal tube and ventilating through the chamber.

The therapeutic effectiveness of an aerosol depends not only on the quantity of drug reaching the lung but also on particle size, best described by the MMAD. MMAD is the diameter above and below which 50% of the mass of the particles is found. Particles less than 5 μm are more likely to deposit in the distal airways whereas larger particles impact on the larger diameter airways.[14] Although the optimum aerosol size for neonates is unknown, theoretical models suggest a similar patterm of deposition to adults.[15] In the past, ultrasonic nebulisers have been bulky and have produced a highly variable output containing significant numbers of large droplets.[16] In this study the combination of both the Pentasonic and Aerochamber with an endotracheal tube produced high quality aerosol. The size distribution of aerosol generated by the Pentasonic was similar to that produced by jet nebulisation.[11] The MMAD of particles generated within the Aerochamber was larger (9 μm), as measured by the imperfect multidose impactor model, but a significant proportion of the aerosol was below 5 μm.

The Pentasonic and the Aerochamber were clinically easy to use. The Aerochamber fitted directly onto the standard Portex endotracheal tube connector without adaption and there were no problems in ventilating infants through the spacer. The Pentasonic could be inserted into the inspiratory line with minimal adaption. There was no change in ventilator pressures during ultrasonic nebulisation and no drop in gas temperature, as measured by a thermister sited in the endotracheal tube connector. It was important to remove the one way valve from the Pentasonic to allow any build up of pressure in the circuit to be vented through the emergency inspiratory blow off valve. The 145 ml Aerochamber temporarily increased the ventilator dead space, and for this reason, we preferred to insert the device briefly, and not to try to maintain mechanical ventilation with the spacer in place. However, spacers are important when using a MDI in ventilator circuits. Particles are ejected from the MDI canister with high velocity and mass.[17 18] As the propellants evaporate particles decrease in size toward the respirable range (<5 μm).[18] If generated near a surface, the large particles will impact and will be wasted. A spacer gives time and distance for particle shrinkage as well as acting as a large particle filter.[19] Removing the spacer may shift the impaction of up to 80% of the aerosolised dose from within the device to the endotracheal tube. Although an endotracheal tube may function as a form of spacer,[11] impacted particles may be washed down into the lung during routine nursing care.

Ultrasonic and MDI aerosolisation have merits and drawbacks. MDIs can effectively aerosolise solutions and suspensions but contain surfactants and propellants, a proportion of which will be deposited within the neonatal lung. MDI drug delivery is also limited by the commercial availability of canisters, but has the potential for rapidly delivering higher doses. Ultrasonic nebulisers can nebulise any solution but is far less efficient in nebulising viscous suspensions such as topical steroids.[20]

Therapeutic doses of sodium cromoglycate can be delivered by both systems. In older non-intubated children, 0·26% of a 20 mg dose of sodium cromoglycate generated by MDI and spacer (Medic Aid) will reach the lungs.[21] For a 10 kg infant this represents a pulmonary dose of 5·2 μg/kg. For an adult, assuming 10% pulmonary deposition, a dose of 20 mg delivers 20–40 μg/kg via the lungs. The mean dose delivered to ventilated neonates by the Pentasonic was 107 μg/kg (range 64–213) and by Aerochamber 234 μg/kg (range 88–394).

In conclusion, this study has demonstrated that the Pentasonic ultrasonic nebuliser and the Aerochamber spacer with MDI are both able to deliver aerosolised sodium cromoglycate to ventilated neonates without the disadvantages of jet nebulisation. There was good agreement between the sodium cromoglycate dose predicted from a filter model and the estimated dose delivered in vivo and may therefore be the method of choice in evaluating future delivery systems. The clinical effectiveness of drugs delivered by ultrasonic nebulisation or MDI remains to be determined.

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Treatment of severe persistent pulmonary hypertension of the newborn with magnesium sulphate

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Abstract

Eight of nine newborn infants with severe persistent pulmonary hypertension of the newborn (PPHN), and a predicted mortality of 100%, and one infant with a predicted mortality >94% based on alveolar–arterial oxygen tension difference ($(A-a)Do_2$) were treated with magnesium sulphate ($MgSO_4$) as a life saving therapy after they failed to improve with conventional treatment. Magnesium at high serum concentrations decreases pulmonary pressures and is a muscle relaxant and sedative. Diluted $MgSO_4.7H_2O$ solution (200 mg/kg) was given intravenously over 20–30 minutes. No changes in the treatment were made after $MgSO_4$. Mean serum magnesium concentration was maintained between 2·88 and 5·67 mmol/l by continuous intravenous infusion (six infants). Baseline arterial oxygen tension (Pao_2) and haemoglobin oxygen saturation had mean (SD) values of 4·66 (1·8) kPa and 60·4 (29·7)% respectively, which started to increase one hour after $MgSO_4$ infusion, and increased significantly at six hours to 12·04 (7·07) kPa and 91·8 (10·88)% respectively. Arterial carbon dioxide tension ($Paco_2$) decreased and pH increased significantly after one hour compared with the baseline value. Pao_2 increases are probably secondary to a decrease in pulmonary vascular resistance and pressure, decrease in a right to left shunt, better ventilation:perfusion ratio, and $Paco_2$ decrease and pH rise. Seven infants survived (77·8%). These results demonstrate the beneficial effect of magnesium in the management of PPHN when other accepted treatment fails, is contraindicated, or not available.

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Persistent pulmonary hypertension of the newborn (PPHN) is characterised by a suprasystemic pulmonary vascular resistance and pressure causing a right to left shunt, and marked hypoxaemia and acidosis which may produce further pulmonary vascoconstriction. In severe cases mortality rate is changing with time and ranges from 10% to 60% despite aggressive management.[1–5] Infants with an alveolar–arterial oxygen difference ($(A-a)Do_2$) more than 82·7 kPa (620 mm Hg) have been reported to have 100% mortality, and those with $(A-a)Do_2$ ≥81·3 kPa (610 mm Hg) for eight hours 80% mortality.[4–6]

PPHN has a wide aetiological diversity which means that no single treatment may be uniformly effective.[1–12] Mechanical hyperventilation, high frequency oscillatory ventilation, vasodilators such as tolazoline and prostaglandins, muscle relaxants, and sedatives have all been advocated.[1–12] Extracorporeal membrane oxygenation has been used to treat severe cases of PPHN with various success,[3 6 7 11 12] but is not available in most neonatal centres. To date no controlled studies have been performed objectively to test the efficacy of the various treatments.

At high serum concentrations magnesium is a potent vasodilator, muscle relaxant, and sedative.[13–16] Previous studies showed that magnesium can prevent and reduce hypoxia induced pulmonary hypertension.[17–19] Eight infants with severe PPHN and a predicted mortality of 100% and one infant with a predicted mortality >94% based on $(A-a)Do_2$ criteria were treated with magnesium sulphate ($MgSO_4$) as a life saving therapy after they failed to improve with conventional treatment when extracorporeal oxygenation and oscillatory ventilation were not available.

Methods and subjects

In our unit, newborn infants with PPHN are treated by conventional methods.[1–4 20] Nine infants with a clinical and laboratory picture consistent with PPHN[1–3 20] failed to improve with conventional management after a period ranging from 15 to 92 hours (tables 1 and 2). Congenital heart disease was excluded in all infants by echocardiography. $(A-a)Do_2$ was greater than 84·3 kPa (630 mm Hg) in eight of nine infants, and was 82·1 kPa (616 mm Hg) in one infant (table 3). By published criteria all were considered candidates for extracorporeal membrane oxygenation.[6 12] $(A-a)Do_2$ was calculated using the following formulas:

$$(A-a)Do_2\ (kPa)=101{\cdot}33\times Fio_2-Pco_2+(Pao_2+6{\cdot}27)$$

$$(A-a)Do_2\ (mm\ Hg)=760\times Fio_2-(Pco_2+Pao_2+47).$$[2–6]

(Where Fio_2 is fractional inspiratory oxygen, Pco_2 is carbon dioxide tension, and Pao_2 is arterial oxygen tension.)

Clinical characteristics of these infants are described in table 1. All infants had normal serum magnesium, urea nitrogen, and creatinine values. Initial treatment is summarised in table 2, and the clinical and laboratory values for individual infants before $MgSO_4$ treatment (baseline) is presented in table 3.

Magnesium sulphate heptahydrate ($MgSO_4.7H_2O$ from Abbott Laboratories) was given as compassionate treatment. Approved hospital procedures for compassionate treatment were

Table 1 Clinical characteristics, diagnosis, and complications before $MgSO_4$ treatment

Patient No	Gestation (weeks)	Birth weight (g)	Outcome	Diagnosis and complications
1	40	2850	Survived	Diaphragmatic hernia, pulmonary haemorrhage, pneumothorax
2	42	3400	Survived	Perinatal asphyxia, MAS, cephalhematoma
3	42	2580	Survived	Perinatal asphyxia, MAS, SGA, sepsis, pulmonary haemorrhage, pneumothorax
4	40	3500	Survived	Perinatal asphyxia, MAS, sepsis
5	32	2240	Survived	Perinatal asphyxia, HMD, polycythaemia, probable sepsis
6	33	2400	Died	Perinatal asphyxia, probable sepsis, gastric and pulmonary haemorrhage
7	41	2880	Died	Perinatal asphyxia, MAS, pneumothorax
8	32	1770	Survived	Perinatal asphyxia, intracranial bleed, seizures, bilateral pneumothorax
9	38	2450	Survived	Diaphragmatic hernia, cleft lip and palate, SGA, pneumothorax

MAS, meconium aspiration syndrome; SGA, small for gestation; HMD, hyaline membrane disease.

followed. Each individual case was discussed by at least two neonatologists, approved by the chairman of the department, and informed consent from the parents was then obtained. Each gram of $MgSO_4.7H_2O$ contains 4·06 mmol magnesium. $MgSO_4$ 50% was diluted to 8% concentration in 5% dextrose solution. An average bolus dose of $MgSO_4$, 200 mg/kg body weight, was given intravenously over 20–30 minutes; one infant received the bolus dose intramuscularly. A continuous intravenous drip of $MgSO_4$ 20–50 mg/kg/hour) was given with the same solution for six infants. Prostaglandin E_2 (PGE_2, tolazoline, and pancuronium were discontinued before $MgSO_4$ was given. No other medications or changes in the ventilator settings or FIO_2 were made after $MgSO_4$ was given except when PaO_2 rose to high values; FIO_2 and ventilator settings were then reduced. Blood gases, magnesium, calcium, electrolytes, and vital signs were measured before $MgSO_4$ was given and periodically thereafter. Arterial blood gases were measured from samples drawn from the umbilical artery (postductal) with a Corning blood gas analyser, and $(A-a)DO_2$ was calculated.

Results are given as mean (SD) for all infants unless indicated otherwise. One sample paired t test was used to compare values two hours before $MgSO_4$ infusion and at various intervals after infusion, with the baseline values measured directly before $MgSO_4$ infusion. Percentage change was calculated as the difference between the value at a certain interval and the baseline value, divided by the baseline value, and multiplied by 100. The χ^2 test with Yates' correction, Fisher's exact test, two tailed test and confidence intervals were used to compare rates. Kruskal-Wallis one way analysis by ranks was used when appropriate.

Results

Serum magnesium concentration increased significantly 1 hour after the supplement, giving values of mean (SD) from 0·7 (0·1) mmol/l to 4·0 (2·2) mmol/l ($p<0·01$). Mean magnesium values during the first 8 hours varied from 2·88 to 5·67 mmol/l.

Umbilical arterial blood PaO_2 for the individual infants and the mean for all at the various intervals are shown in fig 1. For arterial blood gases, the mean percentage change from the baseline and 95% confidence intervals (CI) are shown in fig 2. The mean (SD) of the value for PaO_2 2 hours before $MgSO_4$ infusion was similar to that at the baseline, being 5·47 (2·49) and 4·66 (1·80) kPa respectively ($p<0·459$). PaO_2 started to increase within 1 hour after $MgSO_4$ to

Table 2 Summary of treatment, ventilator settings, and duration before $MgSO_4$ treatment

Patient No	Drugs				Mechanical ventilation				
	Tolazoline	PGE_2	Pancuronium	Dopamine	Rate (per min)	PIP (cm H_2O)	PEEP (cm H_2O)	FIO_2	Duration (hours)
1	Yes	No	Yes	Yes	110	35	3	1	50
2	No	No	Yes	No	60	35	5	1	46
3	Yes	No	Yes	Yes	90	50	5	1	92
4	No	Yes	No	No	80	30	3	0·95	52
5	No	No	No	No	70	30	3	1	30
6	Yes	No	No	Yes	100	35	3	1	21
7	Yes	No	No	Yes	101	30	4	1	15
8	Yes	No	No	Yes	80	28	4	1	48
9	No	No	No	Yes	80	38	2	1	32

PIP, positive inspiratory pressure; PEEP; positive end expiratory pressure, FIO_2, fractional inspiratory oxygen pressure.

Table 3 Initial clinical and laboratory values for individual infants before $MgSO_4$ treatment. Mean blood pressure values are shown

Patient No	Serum magnesium (mmol/l)	Heart rate (bpm)	Blood pressure (mm Hg)	pH	$PaCO_2$ (kPa)	PaO_2 (kPa)	Oxygen saturation (%)	$(A-a)DO_2$ (kPa)
1	0·6[illegible]	154	46	7·47	5·87	4·27	67	84·93
2	0·6[illegible]	141	60	7·35	5·2	3·73	49	86·13
3	0·6[illegible]	136	78	7·56	3·33	6·93	92	84·80
4	0·9[illegible]	150	72	7·15	6·27	1·87	12	82·13
5	0·6[illegible]	147	64	7·38	4·53	6·0	81	84·53
6	0·8	171	46	7·08	7·33	2·27	13	85·47
7	0·5[illegible]	120	52	7·42	2·8	4·67	71	87·60
8	0·6[illegible]	148	29	7·19	4·93	6·4	75	83·73
9	0·6[illegible]	134	41	7·51	4·40	5·73	84	84·93
Mean	0·7	144	54·2	7·35	4·90	4·66	60·4	84·97
SD	0·1[illegible]	14·3	15·66	0·17	1·43	1·8	29·7	1·47

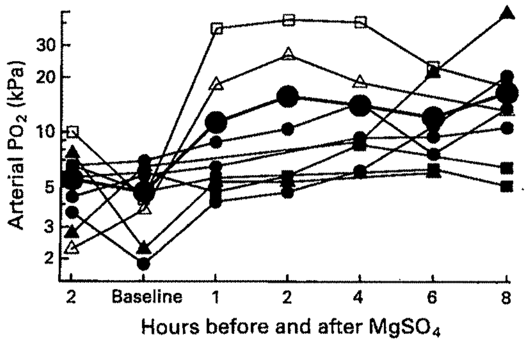

Figure 1 PaO_2 changes before and after $MgSO_4$ treatment for individual infants. Each line represents one infant, the mean for all the infants treated is shown as wide solid line with solid circles.

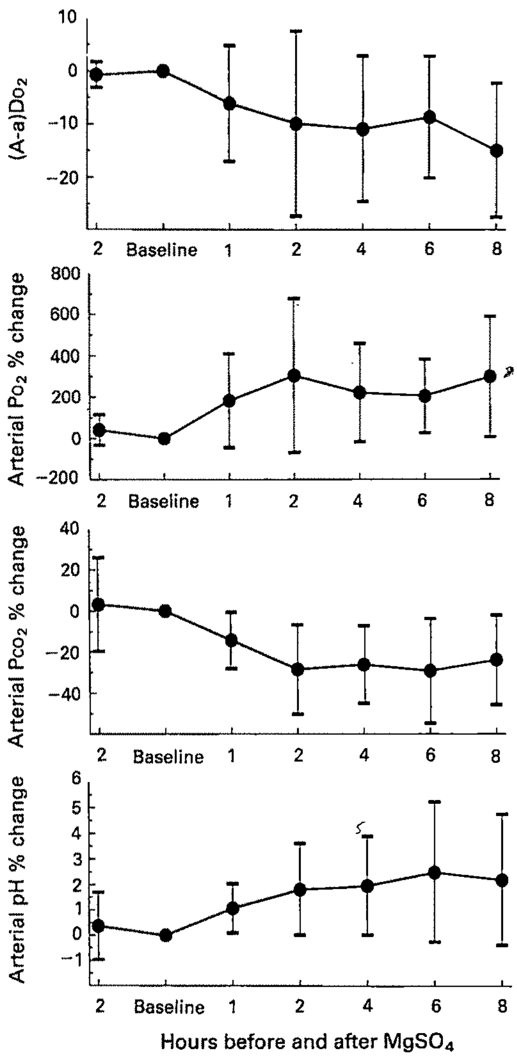

Figure 2 Mean and 95% confidence intervals of percentage change in the arterial blood gas values before and after MgSO$_4$ treatment for all infants.

11·29 (11·41) kPa (p<0·137), mean percentage change was 181·4% and CI was −45·65 to 408·49. At 2 and 4 hours, Pao$_2$ showed a trend to be higher than baseline (p<0·12 and p<0·06 respectively). Pao$_2$ was significantly higher at 6 and 8 hours, with values at 12·04 (7·07) kPa (p<0·029) and 16·47 (12·63) kPa (p<0·035) respectively, and percentage mean change (and CI) from the baseline of 203% (26 to 379%) and 294% (6 to 582%) respectively. Kruskal-Wallis one way analysis by ranks showed that Pao$_2$ had changed significantly during the study period (p<0·004).

Mean (SD) haemoglobin oxygen saturation at 2 hours before MgSO$_4$ infusion was similar to baseline (64 (27)% and 60 (30)% respectively; p<0·78). Saturation increased significantly within 1 hour after MgSO$_4$ infusion to 84 (18)% (p<0·017) and at 8 hours to 95 (6)% (p<0·02). Percentage change (and CI) were 130% (−27 and 288%) and 119% (−87 to 325%) respectively.

Paco$_2$ means (SD) were similar at 2 hours before MgSO$_4$ and at the baseline (4·75 (0·89) and 4·9 (1·43) kPa respectively), and decreased to 4·07 (0·78) kPa (p<0·048) and 3·29 (0·89) kPa (p<0·04) at 1 and 8 hours respectively, mean percentage change and CI being shown in fig 2. Mean (SD) values of arterial pH at 2 hours before MgSO$_4$ infusion and the baseline were 7·37 (0·1) and 7·35 (0·17). Arterial blood pH showed a significant increase at 1, 2, and 4 hours after infusion (p<0·034, p<0·046 and p<0·045) and showed a trend to be higher at 6 and 8 hours, p<0·066 and p<0·08 respectively, mean percentage change and CI being shown in fig 2. Comparing bicarbonate and base excess values during the study period and the baseline did not reveal significant changes. Means (SD) of arterial blood bicarbonate 2 hours before MgSO$_4$, at the baseline and after 8 hours were 20·5 (5·6), 20·1 (6·9), 20·4 (4·6).

(A−a)Do$_2$ started to decrease from the baseline (85 (1·5) kPa) within 1 hour after MgSO$_4$ (80 (11·1) kPa, p<0·89) and was significantly lower after 8 hours 72·2 (13·2) kPa, p<0·025), mean percentage change and CI being shown in fig 2. Seven infants (77·8%) survived while on treatment; in the two infants who died a small decrease in (A−a)do$_2$ was seen initially but it remained greater than 82·67 kPa (620 mm Hg) until they died. One infant died seven days after stopping MgSO$_4$ treatment. None of the infants who died responded to tolazoline and dopamine treatment.

Heart rate 2 hours before MgSO$_4$ was similar to the baseline value: means (SD) were 142 (22) and 145 (14) beats/minute (bpm) respectively. Heart rate showed a trend to decrease during the study period. After 1 and 8 hours the heart rate was 143 (12) bpm (p<0·66) and 129 (14) bpm (p<0·089), but not below 116 bpm in any surviving infant during the study period.

Baseline mean blood pressure for all infants was similar to that at 2 hours before MgSO$_4$ infusion, the values being 54·2 (15·7) and 54 (13·6) mm Hg respectively. Although mean blood pressure showed a trend to decrease at 2 hours after MgSO$_4$ infusion to 47·1 (15·1) mm Hg (p<0·08), it did not show any significant change during the 8 hour period. At 8 hours blood pressure was 51·4 (11·8) mm Hg. No significant changes were observed during the study period in the serum electrolytes and calcium.

Ultrasound scans were taken of the head in all infants and none developed intracranial haemorrhage during treatment. Patient 8 who had had severe perinatal asphyxia and had been successfully resuscitated from a cardiac arrest at 2 days of age, before MgSO$_4$ treatment, had an intraventricular haemorrhage and subsequently developed hydrocephalus. Patient 4 had normal head scans before and at two and seven days after treatment but showed an old infarct lesion in the left frontal lobe in a follow up computed tomographic scan of the brain one month after the treatment. Patient 3 subsequently developed bronchopulmonary dysplasia. No infant had any bleeding from gastrointestinal and urinary tract or through the endotracheal tube during the study period.

Discussion

Drugs that are specific pulmonary vasodilators and reduce pulmonary hypertension are not available yet for clinical use. Pulmonary vasoconstriction depends on the availability of calcium to the affected cells,[21 22] and therefore calcium channel blockers have been tried to induce pulmonary vasodilatation. Magnesium is nature's calcium antagonist: it is a muscle relaxant, vasodilator, sedative, and antithrombotic.[13 14 23–29] Cropp showed in dogs that increase in blood magnesium to 5–6 mmol/l will block hypoxic pulmonary vasoconstriction without causing deleterious changes in haemodynamics or pulmonary ventilation.[17] Paidas showed that continuous infusion of ATP and magnesium chloride produced a significant decrease in mean pulmonary artery pressure after induced hypoxia, but magnesium chloride had no effect when infused alone[18]; but the doses given were very small and magnesium chloride values in the blood were not measured. Abu-Osba *et al* showed in anaesthetised sheep that a sharp increase in the mean pulmonary artery pressure occurred by breathing 10% oxygen, but during hypoxia it fell suddenly to the baseline after $MgSO_4$ infusion.[19] No significant change in the cardiac output was observed, and the heart rate decreased transiently. In contrast, no change was observed after placebo infusion. Magnesium aspartate hydrochloride oral therapy has been shown by Mathew *et al* to attenuate monocrotaline induced pulmonary hypertension, right ventricular hypertrophy and pathological changes in the pulmonary vasculature in rats.[30] Howel and Carrier showed that in rabbit, magnesium reduces the contractile responses of the pulmonary artery to noradrenaline and histamine and alters the sensitivity to histamine.[31] These studies demonstrate the beneficial effect of magnesium in reducing pulmonary hypertension.

$MgSO_4$ has been used for several decades to treat toxaemia of pregnancy. During treatment maternal serum magnesium concentration is 2–3·5 mmol/l and magnesium ions cross the placenta promptly to achieve equilibrium between the mother and the fetus.[26] Side effects of hypermagnesaemia, which has beneficial therapeutic applications in infants with PPHN, include: central sedation, muscle relaxation, hyporeflexia, and decreased excitability.[27 28 32 33] Possible undesirable side effects include calcium and potassium disturbances.[27 28 34] Frequent monitoring of blood concentrations and appropriate supplementations will prevent these complications. Abdominal distension may occur, with absence of bowel sounds. Infants with PPHN usually have a gastric tube inserted and connected to low pressure suction or free drainage and usually they are not fed enterally. High serum concentrations of magnesium may produce respiratory depression, a non-consequential effect in these mechanically ventilated infants. The $MgSO_4$ dose we used and the serum values were similar to that used in toxaemia of pregnancy which has been proved to be safe for both the fetus and the newborn infant.[26–28 32]

Ideally, a controlled double blind study should have been done to test the efficacy and safety of this treatment. Our study was not controlled and our justification was that all the infants were treated with $MgSO_4$ on a compassionate basis after all other available treatment had failed to relieve the severe hypoxaemia and they were expected to die (according to the accepted criteria of $(A-a)Do_2$ used in various studies). There are no pilot studies in humans showing that $MgSO_4$ can treat PPHN, although there is good theoretical and experimental evidence to support this. As the incidence of PPHN is very low it will require a long period to conduct a randomised controlled study unless a multicentre study is organised.

Carter *et al* reported 22 of 25 patients survived (88%) with $(A-a)Do_2 \geqslant 80$ kPa (600 mm Hg): they required extracorporeal membrane oxygenation treatment after failure of high frequency oscillatory ventilation and conventional therapy.[3] Dworetz *et al* reported survival rates in patients eligible for extracorporeal membrane oxygenation based on $(A-a)Do_2 \geqslant 81{\cdot}33$ kPa (610 mm Hg) for eight hours with a predicted mortality 80%.[2] In 1980–1 survival rate was 0% (0/5) and 1986–8 survival rate was 89% (8/9). Although our patients were more severely ill, with $(A-a)Do_2 > 82{\cdot}67$ kPa (620 mm Hg) in eight (predicted mortality 100%) and 82·13 kPa (616 mm Hg) in one patient (predicted mortality 94%), the survival rate in our study was 77·8% (7/9), which is comparable with Carter *et al* and Dworetz *et al.*[2]

Though we did not measure the pulmonary pressure, we suggest that the observed increase in Pao_2 and haemoglobin oxygen saturation is probably secondary to the vasodilator effect of magnesium on the pulmonary vessels. The relief of hypoxaemia, the continuing effect of magnesium, muscle paralysis, and the expected improvement in ventilation: perfusion ratio, could be reasons for $Paco_2$ decreases and pH increases which then lead to further improvement in oxygenation.

Several prostaglandins have been used to decrease pulmonary hypertension.[8–10] $MgSO_4$ has a powerful effect on the production and release of several prostaglandins, especially PGI_2 and its metabolite 6-keto-$PGF_{1\alpha}$. Nadler and Rude have shown in normal human subjects that $MgSO_4$ infusion increases significantly the excretion of the stable PGI_2 metabolite 6-keto-$PGF_{1\alpha}$.[35] Watson *et al* have reported that $MgSO_4$ increases the release of PGI_2 by cultured human umbilical vein endothelial cells (HUVEC); PGI_2 production was two to five times greater when HUVEC were incubated with plasma from preeclamptic patients undergoing $MgSO_4$ therapy than when HUVEC were incubated with pretherapy plasma.[36] Also, $MgSO_4$ enhances by 20–36% the prostacyclin liberation from the umbilical cord vascular wall.[29] Furthermore, magnesium increases production of prostacyclin or its metabolite 6-keto $PGF_{1\alpha}$ in other organs, for example cardiac muscle[37] and antrum and duodenum.[38] Magnesium increases PGI_2 production, decreases PGD_2 production,[38] and depresses the vascular contractions induced by PGF_2.[39] There is evidence that magnesium acts directly on the PGF_2 (vasodilator) receptor site.[40]

The therapeutic effect observed in the infants with PPHN is possibly due to one or a combination of effects of magnesium on production, release, metabolism and receptor sites of prostaglandins. Some reports describe a beneficial magnesium vasodilator effect and reduction of complications after ischaemic hypoxia in the central nervous system, in ischaemic heart disease, and in kidney and liver conditions[16 35 41–43] which frequently coexist with PPHN in the severely hypoxaemic neonate. This study and others suggest the possible benefits of magnesium treatment in PPHN when conventional therapy fails and alternative modes of therapy, for example, extracorporeal membrane oxygenation and high frequency oscillatory ventilation are not available or are contraindicated. A controlled multicentre study is required before recommending magnesium as primary treatment and further work is needed to clarify its mechanism of action in PPHN. Close monitoring of blood pressure, kidney function, electrolytes, glucose, and calcium should be observed and long term follow up is needed.

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Measurement of plasma volume in neonates

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Abstract

There is no reliable and safe method for measuring plasma volume in ill newborn infants. We describe an adaptation of the dye dilution technique using indocyanine green as the plasma label, which can be used in the sickest and smallest of infants with the minimum of disturbance. To avoid the need to take large volumes of blood from the infant, samples were diluted 1:1 with distilled water and pooled adult sera was used to construct the dye dilution standard curves. Eighteen preterm and fullterm infants were studied on 30 occasions. The measured plasma volume ranged between 21·4 and 106 ml/kg. Paired measurements were performed within 30–90 minutes of each other in seven infants. In five infants estimations of plasma volume were made shortly before and 30 minutes after the infusion of a known quantity of plasma. In eight out of 12 infants who had two measurements made there was close agreement between the second measured volume and the first measured volume, taking into account how much plasma had been given to or taken from the infant between the two measurements. The error ranged from 0·2 to 5·2 ml and the plasma recovery error ranged from −2·9% to +4·7%. In the remaining four infants the errors ranged from 2·1 to 9·5 ml and −14·2% to +8·8%. Errors in the measurement of plasma volume may arise as the result of sampling too early before full mixing of the dye has occurred, and there is a potential error in the measurement due to the distribution of albumin in the extracellular space in sick infants resulting in an overestimation of the plasma volume. Proposals for reducing sources of errors are discussed.

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The sick newborn infant is particularly prone to compartmental fluid shifts resulting in fluid and electrolyte imbalances. Fluid balance is clinically assessed in the neonate by measurement of electrolytes and osmolalities in the serum and urine, as well as urinary output and changes in body weight. In some infants who develop renal impairment, cardiac failure, or severe oedema the fluid and electrolyte management may become extremely difficult. In adults, or sometimes in larger infants, invasive central venous pressure monitoring may be used as a guide to intravascular filling. This is rarely technically feasible in the preterm neonate and there are no normal reference values available for this measurement.

An alternative approach to assessment of circulating plasma volumes is the injection of plasma dyes and the measurement of resulting dilutions.[1–3] In neonates, radiolabelled albumin and Evans' blue have been used for this purpose.[4–9] Evans' blue is no longer commercially available and the use of radiolabelled albumin in neonates is restricted by ethical considerations to exceptional circumstances and certainly may not be used repeatedly. An alternative dye, indocyanine green (ICG) has been used in adults, in children with cardiac conditions, and in veterinary practice[10–13] and has been shown to be safe. It has been used in adults specifically to measure plasma volume and the method validated against radiolabelled albumin measurements.[10]

The purpose of this pilot study was to adapt the ICG dye dilution method of measuring plasma volume to small and sick neonates, in whom the greatest constraint is the volume of blood which may be taken for measuring the dye's dilution in the circulation.

We are specifically concerned with the measurement of plasma volume. Alternative methods may be employed for directly measuring red cell mass using a red cell label. An approximation to the red cell mass and thus total blood volume may be made from the plasma volume measurement and the corrected total body packed cell volume.[1 6]

Methods

THEORY

The principle of measuring circulating volumes by dissolving a known quantity of dye and measuring the resulting concentration is essentially simple, but there are a number of theoretical considerations[1] and in the preterm subject a number of practical considerations which have to be overcome.

If a known quantity of solute, Q, is dissolved in volume V, the resulting concentration is C, such that $C=Q/V$ and $V=Q/C$. However, the solute or dye must mix and be evenly distributed throughout the entire volume. In the human circulation, different organ systems will have different circulation times and therefore there will be a phase when the dye concentration measured in the central circulation will be fluctuating before the concentration comes to an equilibrium throughout the entire body. The time taken for the dye to reach this equilibrium is known as the mixing time. An absolute criterion for complete mixing is difficult to establish, but a realistic point for a temporary dye, such as ICG, is taken when there is a constant rate of decline in the dye concentration in the central circulation.[1] The mixing time would theoretically be influenced by the dye indicator used and the state of the patient (for example, cardiac output, blood volume, and splenomegaly). In adult humans the mixing time for ICG has been shown to be in the order of 60 seconds.[10]

Once the dye has been injected it will be lost from the circulation, either to the extravascular compartment or by excretion. If the concentration of the dye could be measured constantly from the moment it was injected, and plotted against time, there would be a periodic fluctuation in the dye concentration for the duration of the mixing time, superimposed upon an exponential decline in concentration due to loss of dye from the circulation (fig 1).

The concentration value that must be known for the equation $V=Q/C$ is the concentration of the dye in equilibrium throughout the entire body system before any of the dye is lost. This may be found by plotting on a log scale the exponential decay curve of the dye, after the mixing time is complete. This will produce a straight line, which on reverse extrapolation to time zero will provide the log value of the required concentration. Theoretically, at this time no dye will have been lost and it will be evenly distributed throughout the body.

Radiolabelled albumin markers have generally been considered the best method of measuring plasma volume, partly because albumin is considered less likely to leak from the circulation. ICG is strongly bound to albumin and thus is a good marker of plasma volume.[14 15] In a sick neonate there is likely to be considerable capillary leakage, but extrapolation of the decay curve to time zero makes allowances for this loss. The steeper the decay curve the more rapidly the dye is being lost. This method for calculating a value for C and thus V has been shown in adults to correlate well with the radiolabelled albumin method.[10]

In those disease states where transcapillary leakage is marked it has been postulated that plasma volume measurements made using albumin markers will overestimate the result because the albumin in these very leaky patients is distributed throughout the extravascular as well as intravascular compartment.[14] Extrapolation back to time zero will make allowances for the leak of albumin out of the circulation but not for the theoretical leak back into the circulation of albumin from the extravascular space. The size of this shifting albumin pool or its speed of circulation is not known. Various studies of plasma volume in adults in whom capillary leakage is expected to be pronounced, such as after cardiac surgery, have been undertaken either comparing albumin measurements of plasma volume and derived values from red cell volumes and packed cell volumes, or albumin measurements and values measured using larger molecular plasma labels such as dextran. The errors recorded in the overestimation of plasma volume using albumin vary from 1·2% to 10%.[14]

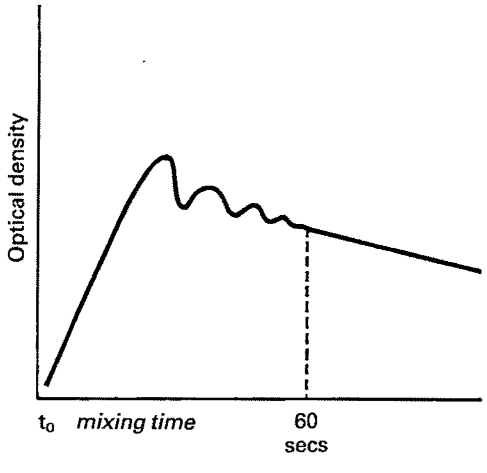

Figure 1 Idealised decay curve for ICG.

Estimates of total blood volume and red cell volume may be derived from the measured plasma volume and a corrected mean body packed cell volume. Conversely plasma volume (PV) and blood volume may be estimated from techniques for measuring red cell volume and a corrected mean body packed cell volume. A measured pack cell volume is not an accurate measure throughout the entire body. For neonates it has been shown that a correction factor of 0·87 should be applied such that mean body packed cell volume ($mPCV=0{\cdot}87\times$measured PCV).[1 6] The cell volume (CV) in ml can be calculated approximately as: $CV=PV\times mPCV/1-mPCV$ and the blood volume (BV) in $ml=CV+PV$.

MATERIALS

ICG was obtained in 25 or 50 mg vials from Becton-Dickenson Microbiology Systems. It is a non-toxic, non-permanent dye which is rapidly removed from the circulation by the liver (half life <10 min), which enables frequent repeated measurements in an individual. It is water soluble with a spectral absorption at 800–810 nm in plasma. Haemoglobin and oxyhaemoglobin do not absorb at these wavelengths, therefore the oxygen saturation does not affect the readings, nor do bilirubin or drugs.

ICG does not stain the skin or mucous membranes. It contains 0·5% sodium iodide and is therefore contraindicated in patients with a history of allergy to iodides; radioactive iodine uptake studies should not be performed for at least a week after the use of ICG. Excretion is impaired by liver dysfunction and it is rapidly bound to albumin. It is contraindicated in jaundice severe enough to require phototherapy. Light fades the dye so all samples must be kept in light proof containers. The aqueous solution is only stable for 10 hours.[10 15]

Standard curve preparations were made from 400 ml of pooled blood donations from two healthy adults. A Pye Unicam SPA-100 dual beam scanning spectrophotometer was used to plot the peak absorption before and after the dilution of samples with water. Subsequent study samples were analysed in a Cecil CE 292 spectrophotometer which requires smaller sample volumes.

PATIENTS

Any infant receiving intensive care requiring both an intravenous and an arterial line for clinical purposes and who was not receiving phototherapy was considered suitable for study. Lipaemic serum interferes with the spectral assay and therefore infants receiving Intralipid (Kabi) were excluded. The study was approved by the hospital ethics committee and informed parental consent was obtained.

A total of 18 infants were studied on 30 occasions. Six of the infants were studied once (group 1), five were studied immediately before and 30 minutes after the infusion of a known quantity of plasma (group 2), and a further seven were studied twice with no infusion of plasma (group 3) 30 to 90 minutes apart. Two of the infants from group 1 were studied for clinical reasons to assess their state of intravascular hydration.

TECHNIQUE

Measurement of plasma volume

The ICG powder was reconstituted in distilled water according to the manufacturer's recommendations. Solutions of 0·25, 0·50, or 1·0 mg/l were prepared such that the volume required to administer 0·2 mg/kg to the baby was between 0·4 ml and 1·0 ml. A dose of 0·2 mg/kg ICG brings the expected concentrations from t_0 to $t_{6\ \mathrm{min}}$ onto the linear part of the standard curve. Before ICG was given, 0·8 ml of blood was withdrawn from the indwelling arterial line: 0·2 ml was used to measure the packed cell volume, the remainder allowed to clot in the dark in a small plain tube. At t_0 the bolus of ICG was injected intravenously and flushed through with water. Three further samples of 0·6 ml were taken into small plain tubes at timed intervals between 1 and 6 minutes after injection and allowed to clot in the dark. The exact time each sample was withdrawn and the total volume of blood taken was recorded.

A portion of the reconstituted ICG was retained for weighing and the preparation of the standard solutions. The syringe used to inject the ICG was weighed before and after the ICG was given to calculate the quantity of ICG given.

Serum was removed from the clotted blood sample, diluted 1:1 with distilled water and the absorbance at 805 nm recorded. ICG concentration was deduced from the water diluted standard curve, and the plasma volume calculated from the equations shown below.

ICG standard curve

A standard curve was produced for each study using sera from the adult pool and the same reconstituted ICG as used in the subjects to eliminate any error in the reconstitution of the ICG powder with distilled water. The reconstituted ICG was further diluted with serum to give ICG standard values of 1·25, 2·50, 5·00, and 10 mg/l. A serum only sample was kept as the blank. Portions of all the standard samples were further diluted 1:1 with distilled water. The optical density measured by the spectrophotometer for each standard sample at 805 nm was recorded and plotted graphically

ICG absorption maximum

Standard solutions and sera taken from subjects after administration of ICG were scanned spectrophotometrically from 750 nm to 850 nm. The blank adult sera (standards) and the infant's serum before ICG were used to provide the zero baseline. All samples were rescanned after a 1:1 dilution with distilled water.

CALCULATIONS

Dose of ICG given

If W, the weight (in mg) of the ICG solution administered; Z, the weight (in mg) of 1·00 ml IGC; and A, the concentration (in mg/ml) of ICG in solution, are all known, then D, the dose (in mg) of ICG to administer can be calculated:

$$D=(W\times A)/Z$$

Plasma volume

Log_e serum ICG concentration is plotted against time. The linear regression line is reverse extrapolated to provide the effective concentration of ICG at time t_0 (ICG_0). Thus PV, plasma volume (in ml) can be calculated:

$$PV=D/ICG_0$$

Plasma recovery

In order to assess the method's reliability and reproducibility we performed paired measurements in a number of infants (groups 2 and 3). In group 2, measurements were made immediately before (PV_1), and 30 minutes after (PV_2) a known quantity of plasma had been infused over a 60 minute period. In group 3, two measurements of plasma volume (PV_1 and PV_2) were made 30–90 minutes apart to see how closely the second volume measurement came to the expected value. Plasma recover (PR) (in %) was calculated as:

$$PR=PV_2/(PV_1\pm \text{ infusion or sample})\times 100.$$

Results

The maximum spectral absorption of both infant and adult serum, either neat or diluted 1:1 with water, was 803–805 nm. Figure 2 shows the decay curves for ICG for one of the infants before and after plasma has been given. The plasma half life of ICG varied from 2·37 to 12·07 minutes, with the longer times corresponding to the larger volumes.

The infants gestational ages ranged from 26 to 41 weeks (median 30 weeks) and their birth weights from 780–3900 g (median 1210 g). The range of plasma volumes was 21·4 to 106·3 ml/kg (median 40·9 mg/kg), see table.

The infant at the lowest extreme of plasma volume was a term, postoperative infant who was very oedematous but had evidence of vascular underfilling with a low urine output and, in this case, a central venous pressure line was in situ recording 2 mm Hg. The infant at

Patient details and results

Patient No	*Birth weight (g)*	*Gestational age (weeks)/postnatal age (days)*	PV_1 *(ml)*	*PV/kg (ml/kg)*	PV_2 *(ml)*	*Net volume given (ml)*	*Error (ml)*	*Plasma recovery (%)*	*Error (%)*
Group 1: Single volume measurement									
1	1780	34/5	68·8	38·7					
2	1960	31/3	99·4	50·7					
3	780	26/3	37·5	48·1					
4	3900	41/1	83·4	21·4					
5	800	31/4	85·0	106·3					
6	2000^E	33/2	81·0	40·5					
Group 2: Before and after plasma infusion (90 min interval)									
7	1200	29/2	53·4	47·7	66·9	15·2	−1·7	97·5	2·5
8	1820	30/1	53·7	29·5	71·8	16·8	+1·3	102·6	2·6
9	780	26/1	26·6	34·1	38·5	9·8	−2·1	108·8	8·8
10	900	26/1	43·5	48·3	53·2	7·3	+2·4	104·7	4·7
11	1040	28/1	42·9	41·3	55·2	8·1	+4·2	108·2	8·2
Group 3: Two measurements—no plasma given (30 min†/90 min interval)									
12	1520	30/1	68·5	45·1	57·2	−1·8*	−9·5	85·8	14·2†
13	1260	30/1	42·5	33·7	36·0	−1·8*	−4·7	87·6	12·4†
14	1100	28/1	44·4	40·3	41·3	−1·8*	−1·3	97·2	2·8
15	1160	28/1	26·7	23·0	22·4	−1·8*	−2·5	89·6	10·4
16	1740	33/1	69·9	40·2	70·2	−1·8*	+2·1	104·0	4·0
17	2500	37/9	148·0	59·2	141·0	−1·8*	−5·2	97·1	2·9
18	1300	28/1	54·8	42·2	53·2	−1·8*	+0·2	100·4	0·4

PV, plasma volume.
E, Expected weight in severely hydropic infant.
*Volume of plasma taken from infant in sampling.
†30 min interval.

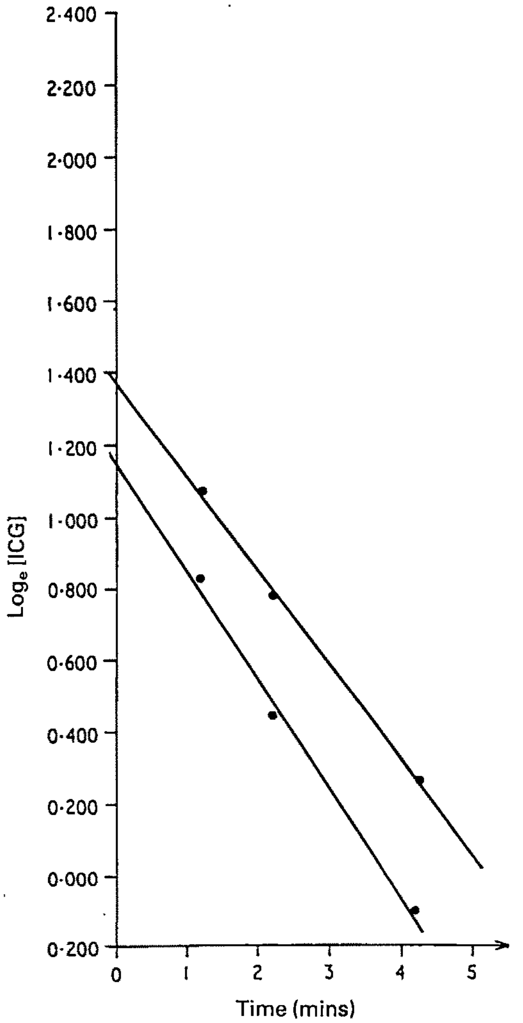

Figure 2 Decay curves from a patient. The top line refers to the preinfusion study and the bottom line to the study after the infusion of 15·2 ml of plasma.

the other extreme was grossly oedematous in established renal failure and was felt clinically to have a fluid overload. An exchange transfusion was undertaken in part to reduce the excessive fluid load.

The net volumes of plasma given to, or taken as samples from, the infants in groups 2 and 3 between the repeated volume measurements ranged from −1·8 to 15·2 ml. The plasma recovery ranged from 85·8% to 108·8%, median 98·9%. The first two infants studied in group 3 had their second volume measurement made 30 minutes after the first, which resulted in the two lowest recovery values (85·8% and 87·6%). By increasing the interval to 90 minutes the mean plasma recovery value for group 3 improved from 97·66% to 98·89%.

No infant suffered any side effect from the study. One patient who was already in extremis from renal failure died eight days after the study. Two other infants died some weeks later from well recognised complications of extreme prematurity.

Discussion

This is the first report of the use of ICG for the measurement of plasma volume in ill neonates. The theory of the dye dilution technique for volume measurements is well documented in the literature. The main practical problem which has to be overcome in applying this dye dilution method to a small neonate is the volume of blood which must be taken from the infant for sampling the dye concentration at varying times and for constructing the ICG optical density standard curve, against which the subject's samples are compared.

To overcome these difficulties in this study the standard curves were prepared using pooled adult sera and all samples were diluted 1:1 with distilled water to reduce the volume of blood required from the infant at each samplng. We demonstrated that neat and diluted sera of both adults and infants had the same absorption spectrum, indicating that these two manoeuvres did not alter the assay results. In further studies we wish to show that differing concentrations of ICG in adult and infant sera behave similarly; we have no evidence to date to suggest that this is not so.

The main source of error in the method arises from the limited number of blood samples that may be taken after ICG injection. We aimed to show that it was possible to make quite reasonable measurements of plasma volume using only three samples after injection to construct the decay curve. A minimum of three points is required to draw the straight line needed for extrapolation back to time zero to make allowance for dye lost from the intravascular space after the ICG injection. To produce an accurate decay plot the three points must be taken after the mixing time is complete, when the decline in dye log concentration falls at a constant rate. Although in adults the mixing time is recorded as 60 seconds, we cannot be certain that in all our infants that this was the case. It is possible that infants with large circulating volumes, or with poor cardiac output or organomegaly, may well have mixing times in excess of the reported 60 seconds in adults. The three points of the decay curve for the infant in renal failure (No 5) fell closely onto a straight line as did the points for the hydropic infant (No 6). No other infant had evidence of organomegaly or poor cardiac output. Initially we sampled at 1, 2, and 4 minutes after ICG injection. We found the scatter of the points on the decay curves improved for sampling times at 2, 3·5, and 6 minutes, implying that the mixing time might be longer than 60 seconds. Sampling cannot be delayed for periods of up to 10 minutes, as used for Evans' blue in adults and infants, because ICG is rapidly removed from the circulation and the resulting concentrations would become unmeasurably small. However, our repeat measurements at 30 minutes compared with those at 90 minutes suggests that clearance in these infants is not as rapid as in an adult.

There is no 'gold standard' measurement of plasma volume in the neonate against which we can compare our results. The median plasma volume of 40·9 mg/kg compares favourably with the results of Linderkamp *et al*, who obtained 40·4–54·8 ml/kg using Evans' blue,[5] and 37·3–53·7 ml/kg using ^{125}I.[4] Mollison, using Evans' blue in 46 term infants, found a range of 30·6–94·8 ml/kg, median 43 ml/kg.[6] It also agrees well with published estimates of plasma volume derived from measurements of red cell volume, blood volume, and packed cell volume. Bentley and Lewis found a mean 41·96±8·86 ml[16]; Jones *et al* found a mean of 38·1±0·6 ml for packed cell volume/red cell volume and 39·5±0·73 ml for blood volume/red cell volume.[17] This agreement may suggest that the theoretical error of overestimating the plasma volume by albumin labels in sick, leaky patients is minimal and of the order inherent in any in vivo analysis.

The wide ranges found in volume measurements may be considered by some to be evidence of error in the method. The infants studied represented a considerable range of clinical conditions from a fluid overloaded infant in renal failure to a grossly fluid restricted postoperative infant, which would make it quite likely that their plasma volumes would not be within what might be considered a normal range. We believe the range found in our study was a true reflection of these infants' varying intravascular volumes.

We are about to install an 805 nm filter to a Cobas Mira (Roche). This micromethod will allow one third less blood to be taken at each sampling. It will mechanise the diluting and assays so that the speed and precision of the method will be enhanced. As smaller volumes are required it will then be possible to take a greater number of samples and so produce more points with which to construct the decay curves and so make the measurement more reliable. It will also be possible to take multiple samples immediately after the injection of ICG to study the mixing time.

This pilot study demonstrates the feasibility of performing repeated plasma volume measurements in the smallest and sickest of infants with the minimum of disturbance. Further refinements of the method are being undertaken to increase the precision and ease of application to routine clinical use.

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IgG subclasses compared in maternal and cord serum and breast milk

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Abstract

Total and specific IgG subclass antibodies against 14 pneumococcal capsular polysaccharide antigens on the cord serum from 11 healthy term infants at birth and on serum from their mothers at delivery were evaluated. The same evaluation was performed five days after delivery on the serum and the milk obtained from the six mothers who were breast feeding their infants. Mean neonatal: maternal serum ratio of total IgG$_1$ was significantly higher than the ratios of total IgG$_2$, IgG$_3$, and IgG$_4$ and higher than the ratios of pneumococcal IgG subclass antibodies. Total IgG$_3$ and IgG$_4$ ratios were higher than the specific antibody ratios of the same IgG subclass. Type 1 and type 14 IgG$_1$ antibodies were the highest antipneumococcal ratios.

Although the maternal milk:serum ratios of total IgG subclasses were very low, significant amounts of specific antibodies were found in the milk, at about half the concentration observed in mother's serum.

Maternal IgG, transferred across the placenta to the fetus during intrauterine life, represents an important component of the neonatal immunological defence mechanisms against infection.[1] IgG$_1$ subclass antibodies are transferred at a greater extent than IgG$_2$, IgG$_3$, and IgG$_4$ due to an active transport process.[2]

Chudwin *et al* reported that the maternal–fetal transfer of total IgG was higher than the transfer of the 7F pneumococcal polysaccharide specific IgG.[3] Soto *et al* showed that higher concentrations of neutralising antibodies to measles, mumps, and rubella viruses were present in cord sera than in paired maternal sera.[4] On the other hand, other researchers could not find significant differences between maternal:fetal ratio of total IgG and specific IgG against either group B streptococcus or *Haemophylus influenzae* (polysaccharide antigens) or tetanus toxin.[5,6]

The aim of the present study was to evaluate the maternal–fetal transfer of total and specific IgG subclass antibodies against 14 pneumococcal capsular polysaccharide antigens. We also evaluated the same antibodies in the milk of mothers who were breast feeding their infants.

Patients and methods

We studied 11 healthy term infants with birth weight from 2760 to 4050 g (mean 3440 g) and gestational age from 39 to 41 weeks (mean 40·2 weeks), and their mothers, aged 18 to 38 years (mean 32 years).

A sample of cord blood was obtained from all infants at birth and a sample of venous blood from all mothers. Five days after delivery a sample of venous blood and of milk were obtained from the six mothers who were breast feeding their infants.

Blood samples were allowed to clot at room temperature and were then centrifuged; aliquots of serum were frozen at −20°C until analysis. Samples of breast milk were centrifuged at 2000 *g* for 10 minutes and the upper lipid and lower cellular fractions were discarded; a second centrifugation at 4500 *g* was then performed for 30 minutes and the middle fraction was collected and frozen at −20°C until analysis.

IgG SUBCLASS DETERMINATION

Total IgG subclasses were quantified by radial immunodiffusion as previously described.[7] Briefly, monoclonal antibodies (Umpath) to IgG$_1$ (clone JL512), IgG$_2$ (clone GOM1), IgG$_3$ (clone 2G4), and IgG$_4$ (clones RJ4+GB7B) were added to agarose 1% in 0·1 M barbitone buffer pH 8·6 containing 6% polyethyleneglycol (PEG 3000, Fluko) at the concentrations of 0·2%, 1·4%, 0·3%, and 0·5%, respectively. Samples to be tested were diluted 1/10 in barbitone buffer for IgG$_1$ and IgG$_2$ and 1/2 for IgG$_3$ and IgG$_4$. Plates were left at 4°C for 48 hours, washed overnight in barbitone buffer containing 2% glutaraldehyde, dried, and stained with Comassie brilliant blue. Results were interpolated from a standard curve constructed using a pool of normal sera calibrated against World Health Organisation reference serum (67/97). Lower sensitivity limits were 0·017 g/l for IgG$_1$, 0·045 g/l for IgG$_2$, 0·01 g/l for IgG$_3$, and 0·064 g/l for IgG$_4$, respectively.

SPECIFIC IgG SUBCLASSES DETERMINATION

Four polyvinyl chloride microtitre plates (M24A Dynatech Laboratories, Virginia) were coated with the capsular polysaccharide types: 1, 2, 3, 4, 6A, 7F, 8, 9N, 12F, 14, 18G, 19F, 23F, and 25 at the concentration of 5 µg/ml in carbonate-bicarbonate buffer pH 9·6, incubating for three hours at 37°C and overnight at 4°C. After three washings, 100 µl of the samples to be tested were diluted 1/50 in bovine serum albumin (BSA) 2% in phosphate buffered saline (PBS), in duplicate, and the plates were incubated for two hours at 37°C. After three washings, 100 µl of IgG subclass specific monoclonal antibodies (clones JL512, GOM1, ZG4, RJ4; Sewards Laboratory) diluted 1/1000 in BSA 2% in PBS were added. After two hours at

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37°C and three washings, 100 µl of peroxidase conjugated rabbit antimouse Ig (Dako) diluted 1/500 in PBS 15% calf serum were added and plates incubated and washed as above. Then 100 µl of freshly prepared substrate solution (50 mg *o*-phenylenediamine with 25 ml phosphate buffer pH 6 and 12·5 µl H_2O_2, 2N) were added to each well and after 20 minutes absorbance was recorded using Titertek Multiskan Photometer (Flow Laboratories) at 492 nm. Results were expressed as percentage of a positive pooled human serum reference. This method is much more sensitive than radial immunodiffusion.

STATISTICAL ANALYSIS

This was carried out by the two way analysis of variance, after logarithmic transformation of ratios, and by the Duncan's multiple range test, to evaluate the difference between mean neonatal:maternal serum ratios and maternal milk:serum ratios of specific IgG subclass antibody concentrations or of total IgG subclass concentrations. Analyses were performed with the Biometrics package (Lionheart).

Results

Mean (SD) for cord and maternal serum concentrations of total IgG subclasses are reported in table 1.

Mean (SD) neonatal:maternal ratios of serum concentrations of IgG subclasses and specific IgG subclass antibodies against pneumococcal capsular polysaccharide antigens are given in table 2. No significant differences were found between mother's specific IgG subclass concentrations before and at five days after delivery.

The two way analysis of variance, performed after logarithmic transformation of ratios, showed a significant difference within the subjects (F=7·32; p<0·0001) and within the ratios (F=2·41; p<0·0001). The standard error of the whole table was 0·2461.

Table 1 Cord and maternal serum concentrations of total IgG subclasses. Results are expressed in g/l and reported as mean (SD)

	IgG$_1$	*IgG$_2$*	*IgG$_3$*	*IgG$_4$*
Cord	7·82 (2·93)	2·54 (0·91)	0·42 (0·21)	0·59 (0·22)
Mother	4·87 (2·17)	3·33 (1·09)	0·47 (0·31)	0·52 (0·20)

Table 2 Neonatal:maternal serum ratios of total and specific IgG subclass antibodies against pneumococcal capsular polysaccharide antigens. Results are expressed as mean (SD)

Types	*IgG$_1$*	*IgG$_2$*	*IgG$_3$*	*IgG$_4$*
1	1·07 (0·32)	0·73 (0·16)	0·82 (0·28)	0·80 (0·31)
2	0·45 (0·41)	0·54 (0·21)	0·35 (0·29)	0·37 (0·36)
3	0·49 (0·60)	0·62 (0·36)	0·51 (0·44)	1·31 (2·09)
4	0·74 (0·54)	0·87 (0·39)	0·87 (0·97)	0·65 (0·43)
6	0·80 (0·76)	0·63 (0·32)	0·45 (0·35)	0·44 (0·68)
7	0·58 (0·31)	1·00 (1·05)	0·50 (0·32)	0·56 (0·37)
8	0·66 (0·45)	0·52 (0·26)	0·47 (0·41)	0·31 (0·31)
9	0·47 (0·38)	0·56 (0·28)	0·48 (0·48)	0·36 (0·42)
12	0·12 (0·27)	0·51 (0·49)	0·17 (0·30)	0·33 (0·4)
14	0·99 (0·40)	0·67 (0·19)	0·51 (0·41)	0·36 (0·31)
18	0·61 (0·41)	0·55 (0·25)	0·26 (0·37)	0·47 (0·52)
19	0·50 (0·43)	0·65 (0·25)	0·58 (0·40)	0·59 (0·36)
23	0·43 (0·49)	0·64 (0·31)	0·63 (0·87)	0·43 (0·30)
25	0·51 (0·26)	0·74 (0·28)	0·46 (0·25)	0·56 (0·29)
Total IgG	1·66 (0·43)	0·78 (0·19)	0·89 (0·46)	1·17 (0·45)

Table 3 Maternal milk: serum ratios of total and specific antipneumococcal IgG subclass antibodies. Results are expressed as mean (SD)

Types	*IgG$_1$*	*IgG$_2$*	*IgG$_3$*	*IgG$_4$*
1	0·13 (0·08)	0·11 (0·07)	0·37 (0·33)	0·28 (0·24)
2	0·72 (0·58)	0·18 (0·14)	0·86 (1·05)	0·66 (0·47)
3	0·37 (0·33)	0·13 (0·21)	0·45 (0·11)	0·48 (0·46)
4	0·48 (0·43)	0·34 (0·38)	2·67 (2·33)	1·20 (1·20)
6	0·44 (0·51)	0·34 (0·27)	1·48 (0·89)	1·49 (1·27)
7	0·64 (0·71)	0·11 (0·12)	0·78 (0·66)	0·78 (0·57)
8	0·46 (0·66)	0·20 (0·15)	0·60 (0·70)	0·76 (0·53)
9	0·96 (1·74)	0·29 (0·17)	0·42 (0·46)	1·09 (0·84)
12	0·45 (0·48)	0·34 (0·45)	0·37 (0·36)	2·04 (2·95)
14	0·15 (0·25)	0·19 (0·14)	1·19 (1·90)	1·01 (0·67)
18	0·15 (0·03)	0·07 (0·09)	0·75 (0·85)	0·75 (0·96)
19	0·27 (0·29)	0·34 (0·34)	0·71 (0·67)	0·83 (0·59)
23	0·98 (1·60)	0·65 (0·71)	0·81 (1·08)	1·27 (0·59)
25	0·12 (0·08)	0·36 (0·25)	0·73 (0·72)	0·99 (0·57)
Total IgG	<0·0034	<0·0066	<0·022	<0·18

The following evaluation by the Duncan's multiple range test (p<0·01) showed that mean total IgG$_1$ neonatal:maternal serum ratio was significantly higher than all the other total and specific IgG subclass ratios; total IgG$_3$ and IgG$_4$ ratios were significantly higher than the specific antibodies of the same subclass (except types 1 and 4 IgG$_3$ and type 3 IgG$_4$); type 1 and 14 IgG$_1$ neonatal:maternal serum ratios were significantly higher than the other IgG$_1$ specific ratios (except types 4 and 6 ratio). Furthermore, type 1 specific IgG$_1$ ratio was higher than type 1 IgG$_2$ ratio; type 14 IgG$_1$ ratio was higher than type 14 IgG$_3$ and IgG$_4$ ratio.

Mean (SD) maternal milk:serum ratios of total and specific antipneumococcal IgG subclass antibodies, evaluated on maternal serum obtained five days after delivery, are reported in table 3. Total IgG subclass concentrations in the milk were always below the lower sensitivity limits of the assay.

The two way analysis of variance, performed after logarithmic transformation of ratios, showed a significant difference within the subjects (F=18·7; p<0·0001) and within the ratios (F=2·58; p<0·0001). The standard error of the whole table was 0·4329.

The following evaluation by the Duncan's multiple range test (p<0·01) showed that the maternal milk:serum ratio of types 4, 6, and 14 IgG$_3$ and types 4, 6, 9, 12, 14, 23, and 25 IgG$_4$ antibodies were higher than the other ratios of specific antibodies.

As concentrations of total IgG in milk were undetectable, maternal milk:serum ratios of total IgG have not been included in the statistical analysis.

Discussion

Maternal IgG transfer to the fetus across the placenta begins at the 16th week of gestation, and is mainly completed during the last six weeks of gestation.[8] The finding of a higher transport rate of IgG$_1$, as compared with IgG$_2$, IgG$_3$, and IgG$_4$, which was previously reported and is confirmed by our study, could be related to a higher trophoblastic receptor affinity for the IgG$_1$ Fc fragment than for the Fc fragment of other subclasses[9] and to an early selective capacity of synthesis by the infant.[10] As for specific IgG transfer, it is controversial whether the neonatal:maternal serum ratio of specific antibodies is higher,[4] similar,[5 6] or reduced[5] as compared with that of total antibodies.

In the present study we found lower neonatal: maternal serum ratios of specific than total IgG_1, IgG_3, and IgG_4 subclasses. Our results are in agreement with those reported by Chudwin *et al,* who evaluated the transfer of total and specific antibodies against 7F type pneumococcal antigen, although with no differentiation in IgG subclasses.[3]

At variance with previous reports,[11 12] we could not observe a restriction of antipneumococcal polysaccharide antigen IgG to the IgG_2 subclass. We found that neonatal:maternal serum ratios of IgG_1 subclass antibodies against types 1 and 14 antigens were higher than ratios of other specific IgG subclass antibodies. As types 1 and 14 pneumococcal polysaccharide antigens are more immunogenic than other types,[13] we can hypothesise that a greater immunogenicity may be important for the modulation of transplacental transfer of antibodies.

Although the maternal milk:serum ratios of IgG subclasses were very low, in agreement with a previous study which reported that less than the 3% of maternal serum IgG is present in the milk,[14] we found significant amounts of specific antibodies in the milk (particularly within the IgG_3 and IgG_4 subclasses), at about half the concentration observed in the mother's serum. This finding could be related to a selective secretion and/or to a local production of antibodies by milk cells.[15] The presence of specific antibodies in breast milk may be considered as a compensatory factor for the reduced maternal–neonatal transfer of specific IgG subclass antibodies.

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Reduced use of surface cultures for suspected neonatal sepsis and surveillance

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Abstract

Data on infection in a neonatal unit were collected prospectively for seven years. After the first four years, the number of surface cultures obtained from neonates with suspected sepsis and for surveillance was reduced. Rates of systemic infection (sepsis and meningitis) were not significantly different in the four years before and the three years after this change. Reduction in surface culture information made no observable difference to detection of colonisation in neonates with early onset sepsis (within first 48 hours of life) nor to antibiotic choice in late onset sepsis. Decisions concerning the length of antibiotic course in suspected infection were not adversely affected. Reduction in the number of surface cultures led to considerable saving of time, effort, and cost while appearing safe in terms of clinical practice and outcome.

The use of surface cultures from neonates on intensive care units is controversial. Early studies suggested that routine surface cultures performed on individual infants at regular intervals as surveillance provided useful predictive information about the causative organism if an infant became septicaemic.[1] This has been challenged in a study by Evans *et al*, who found such cultures to be of little value in predicting the organisms causing true sepsis even if taken at the time of suspected sepsis.[2] Fulginiti and Ray describe surface culturing for the individual infant as an 'exercise in futility, wastefulness and inappropriate practice'.[3] It may, however, be important to perform surface cultures to know what organisms are prevalent in a neonatal unit, their antibiotic sensitivity, and whether they are spreading from baby to baby.[4] Preterm infants who receive artificial ventilation are at most risk of nosocomially acquired infections and comprise more than 80% of such cases,[5] and surveillance cultures could be reserved for these babies. For early onset infection, the infant is usually heavily colonised with the invading organism, and culture from many sites may be unnecessary.

We have prospectively collected data on neonatal infections for seven years. Three years ago, we began an intervention study by reducing the number of surface cultures obtained from neonates for suspected sepsis and for surveillance. Effects on clinical practice and outcome were sought.

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Methods

The neonatal unit serves a maternity department with a delivery rate that has increased from 5750 to 6500 per annum over the seven years of the study and is the regional referral centre. There are approximately 550 admissions to the neonatal unit per annum, with about 10% of babies transferred from other hospitals.

DEFINITIONS AND DATA COLLECTION

Since April 1984, a weekly 'infectious diseases' ward round has been held on the neonatal unit. All microbiology reports for the previous week are collected and positive cultures recorded. All the babies are reviewed and episodes of systemic sepsis or other infection noted. If a baby is discharged during the week, the case notes are reviewed. The level of intensive care required and antibiotics prescribed are also recorded for each infant.

Early onset of sepsis is defined as septicaemia or meningitis in the first 48 hours of life. The unit policy is to stop antibiotic treatment in babies suspected of early onset sepsis if blood and cerebrospinal fluid cultures are negative after two to three days, unless the clinical state remains one of pneumonia or systemic infection in an infant heavily colonised with a pathogen such as group B streptococcus or *Listeria monocytogenes*. This has been termed 'very probable' early onset infection.[6 7]

Late onset sepsis is defined as sepsis or meningitis occurring after 48 hours of age. Unit policy is to stop antibiotics on babies suspected of late onset sepsis if blood and cerebrospinal fluid cultures are negative after two days unless the clinical situation indicates otherwise: either the baby has continued to have signs suggesting systemic infection or a focus of infection has become apparent.

SURFACE CULTURES

In April 1988, we introduced a regimen that decreased the number of surface cultures performed for suspected early and late sepsis (table 1). For the 48 month period from April 1984 to March 1988 (period A) at least six surface sites were cultured, including aspirate of endotracheal secretions if the infant was intubated. For the 36 month period from April 1988 to March 1991 (period B) only two surface sites were cultured for suspected early onset sepsis: the external auditory canal and the throat. The urine was not cultured. For suspected late onset sepsis, no surface sites were cultured, but blood, cerebrospinal fluid, and urine were cultured. Surveillance cultures were decreased in this latter period from three times a week culture of tracheal aspirate from the endo-

Table 1 Changes in surface cultures for babies with suspected sepsis and in surveillance cultures between periods A (1984–8) and B (1988–91)

Reason for culture	*Period A*	*Period B*	
	Early and late onset	*Early onset*	*Late onset*
Suspected sepsis	Blood Cerebrospinal fluid Ear Nose Eye Rectum Umbilicus Urine	Blood Cerebrospinal fluid Ear Throat	Blood Cerebrospinal fluid Urine
Surveillance	Endotracheal or nasopharyngeal (three per week)	Endotracheal (weekly)	

Table 2 Comparison of incidence of early (under 48 hours old) and late onset septicaemia or meningitis between period A (1984–8) when multiple surface cultures were performed and period B (1988–91) when the number of surface cultures had been reduced

	Period A		*Period B*		*p Value*
	No	*Per 1000 live births*	*No*	*Per 1000 live births*	
Early onset sepsis					
Definite	42	1·7	19	1·0	0·058
Detected	38/39* (0·97)		17/18† (0·94)		0·53
(95% CI)	(0·06 to 13·5)		(0·14 to 27)		
Very probable	12	0·5	8	0·4	0·89
(95% CI)	(6 to 21)		(3 to 16)		
Late onset	64	2·6	57	3·0	0·69

*Three not tested, †one not tested. CI, confidence interval.

Table 3 Early onset sepsis: bacteraemia or bacterial meningitis in babies under 48 hours of age, in the neonatal unit 1984–91

	Group B streptococcus	*Listeria monocytogenes*	*Gram negative*	*Other*	*Total*	*Incidence/ 1000 live births*
1984/5	3 (3)	0	3	4	10	1·7
1985/6	5 (4)	1	2	4	12	2·1
1986/7	6 (2)	2	1	4	13	2·1
1987/8	2 (3)	3	0	2	7	1·1
1988/9	3 (4)	3	0	1	7	1·1
1989/90	4 (2)	1	1	0	6	1·0
1990/1	2 (1)	0	2	2	6	0·9

Figures in parentheses are cases of probable group B streptococcal infection (see text for definition).

tracheal tube in ventilated babies and nasopharyngeal secretions from all other babies receiving intensive care, to once weekly culture of only tracheal aspirates from ventilated babies.

Comparisons were sought between periods A and B for rates of infection (early onset, very probable early onset, and late onset sepsis); for cases of early onset sepsis where surface cultures failed to show surface colonisation; for outbreaks of sepsis with resistant organisms missed because of the decreased frequency of surveillance cultures, and for cases of missed sepsis where infants might have had relapse of infection if antibiotics were stopped inappropriately early.

Statistical analysis of significance of differences in proportions was by χ^2 test or by the Fisher's exact test if numbers being compared were insufficient for appropriate use of the χ^2 test.

Results

There was no change in the incidence of early onset infection between the two study periods. No significant change in detection rate occurred after the number of surface cultures was reduced. The false negative rate was similar; cultures from surface sites failed to detect colonisation in one of 38 septic infants in period A, compared with one of 18 infants in period B (table 2). There was no change of incidence in the 'very probable' infection in infants in whom blood and cerebrospinal fluid cultures were negative but who remained clinically infected and had surface cultures showing colonisation (table 2). Aside from those infants with proved sepsis and 'very probable' sepsis, antibiotics were routinely stopped at 48 hours irrespective of surface culture results. No infant subsequently relapsed with infection soon after antibiotics were stopped. The decrease in number of surface cultures from at least six to two did not result in any missed cases of early onset sepsis. The causative organisms are shown in table 3.

The incidence of late onset sepsis was also not significantly different between the two periods (tables 2 and 4). There were no occasions during period B, when less surface culture information was being collected, where an infant relapsed after stopping antibiotics.

During period B, there was one outbreak of infection with an organism resistant to multiple antibiotics. A preterm infant with severe necrotising enterocolitis, bowel perforation, and peritonitis grew *Escherichia coli* from both peritoneal fluid and tracheal aspirate that was resistant to ampicillin, netilmicin, and gentamicin. The weekly culture of tracheal aspirate showed that the infant in the adjacent cot was also colonised with this organism. All neighbouring babies had nasopharyngeal or, if ventilated, tracheal cultures taken to see if further spread had occurred undetected by the once weekly tracheal surveillance culture. No other colonised infants were found. Routine infection control precautions, in particular careful handwashing, were re-emphasised and no further spread to other infants was found. On another occasion, two neighbouring ventilated infants became septicaemic within a few days of each other with a Gram negative organism, *Alcaligenes*

Table 4 Late onset sepsis: bacteraemia or bacterial meningitis in babies over 48 hours old, in the neonatal unit 1984–91

	Gram negative bacillis	*Enterococci*	*Coagulase negative*	*Staphylococcus aureus*	*Other**	*Total episodes*	*Incidence/ 100 live births*
1984/5	14	2	1	0	0	15	2·5
1985/6	12	8	3	0	1	19	3·3
1986/7	8	5	5	1	1	16	2·6
1987/8	8	1	5	0	2	14	2·2
1988/9	2	0	13	2	0	17	2·7
1989/90	7	1	8	2	2	19	3·2
1990/1	3	0	13	2	3	21	3·2

*Other=anaerobes, fungi, other Gram positive organisms; some episodes were polymicrobial.

denitrificans. Culture of the tip of the umbilical arterial catheter from one of the infants grew the organism. As this was an unusual infecting organism, a search was made for a likely source. Sites such as parenteral nutrition bags, sinks, humidifiers, and incubators were cultured. All babies in that particular room of the intensive care unit had their nasopharyngeal or, if ventilated, tracheal secretions cultured. No evidence of environmental or surface colonisation was discovered and no further episodes of sepsis with this organism occurred. The reduction in number of surface cultures to once a week from the endotracheal tube of artificially ventilated infants appeared to give adequate information about the prevailing organisms colonising the most 'at risk' babies on the unit.

Annually, approximately 310 'septic screens' were performed for suspected early onset sepsis and 150 for late onset. On average there were four intubated babies from whom the weekly surveillance culture was collected. Reducing the surface cultures as shown in table 1 and reducing routine surveillance cultures of endotracheal secretions from three times to once per week, led to a fall of 75% in the number of surface cultures from approximately 3800 to 960 per year. We estimated that each surface culture processed in the microbiology unit of this hospital costs £10 (using a time and motion study). The approximate annual saving from reducing the number of cultures was £28 000.

Discussion

Culturing of multiple body surface sites is widely practised in neonatal units.[2] This is done both at the time of suspected sepsis and at frequent intervals as a surveillance of potential pathogens. With increasing length of stay in a unit, a baby becomes sequentially colonised with a number of organisms but colonisation has been shown to correlate neither with the likelihood of occurrence of infection in that particular baby nor with the organism actually causing infection when it occurs.[8–13] Evans *et al*[2] showed that even surface cultures performed on the day of suspected sepsis were poorly predictive of the organism actually causing infection of normally sterile body fluids. The longer the period between culture and infection, the more poorly predictive were the cultures. We have shown in this study that the number and frequency of surface cultures can be greatly decreased without compromising patient care.

One way in which a reduction of surface cultures was effected was to decrease the number of sites cultured at the time of suspected sepsis. Infants with early onset infection acquire the infecting organism from the birth canal either before or during birth. As they are likely to be heavily colonised, it was not unexpected that we found a culture of throat and external auditory canal to be as reliable as the culture of six or more sites previously performed. Colonisation with a potential pathogen at birth does not of itself predict infection. It could be argued that surface culture information is completely redundant. The septic screen is performed on the basis of clinical symptoms and signs of infection and/or recognised risk factors for early onset infection.

A decision to stop antibiotics is usually made at 48–72 hours if blood and spinal fluid cultures are negative and the clinical picture allows. There is a group of babies in whom there is presumptive evidence of infection such as pneumonia but the body fluid cultures are negative. Philip *et al* termed these babies as having 'very probable' infection.[6] It was to detect an aetiological organism for these infants that we retained some surface cultures. With the reduced number of sampling sites, we did not see a change in incidence of prospectively diagnosed cases of 'very probable' infection between the two study periods. However, a much larger study, of approximately 700 patients, would be necessary to have an 80% chance of detecting a change of statistical significance. Urine infection is unusual in the first two days of life.[14] In the first four years of study (1984–8), we had no positive cultures of urine from babies with early onset sepsis, other than as part of generalised sepsis such as group B streptococcal septicaemia, and we therefore decided to stop culturing urine for suspected early onset sepsis.

We abandoned entirely the use of surface cultures for babies with suspected late onset infection in the light of the study of Evans *et al.*[2] Surface cultures on an individual baby do not help in predicting either an infective episode or the aetiology of an actual episode even when the culture site is contiguous with the infected surface—for example, the endotracheal secretions from intubated infants with pneumonia.[12] Our antibody policy for suspected late onset sepsis (a semisynthetic penicillinase resistant penicillin, flucloxacillin, and an aminoglycoside), is based mainly on the organisms which have caused sepsis in the past.[7] The antibiotics used may have to be changed if there are frequent episodes of systemic sepsis with resistant organisms.[4] Sometimes an outbreak with resistant organisms may be predicted by finding widespread colonisation with the organism,[4] although Slagle *et al* found correlation between organisms in endotracheal isolates and those causing systemic sepsis in only 19% of cases.[13] Nevertheless, we have encountered situations where knowledge of endotracheal colonisation, combined with episodes of sepsis with resistant organisms, enabled us to change the antibiotic procedure rapidly.[4]

As it is the smallest, most premature, most intensively nursed infants who are at greatest risk of late onset sepsis,[5] we decided to retain a once weekly endotracheal culture as our sole routine surveillance culture compared with the previous three times weekly cultures. The incidence of late onset sepsis was unchanged in the two periods. In period B, when surveillance was reduced, there were no major omissions in terms of the range of coverage with antibiotics for suspects sepsis.

The study coincided with coagulase negative staphylococci emerging as the single commonest pathogen responsible for late onset sepsis. Forty per cent of these isolates were methicillin resistant (data not shown), though no clinical deterioration occurred before vancomycin was substituted for the semisynthetic penicillin, probably because of sensitivity to the aminoglycoside, and the removal of any central venous catheters. Given the variety and ubiquity of coagulase negative staphylococci colonising infants, the prediction of the invasive isolate by surveillance would have been impossible. The limited surveillance did detect the localised spread between babies of an organism resistant to multiple antibiotics, but more extensive surface culturing failed to detect any further spread. When there was an outbreak of late onset sepsis with an unusual organism, not detected by the once weekly endotracheal culture, nor a part of the prevalent flora, a more extensive search was made (including the use of surface cultures of the babies in the same room as the index case), but no evidence of surface colonisation was found. Both episodes suggested that the limited surveillance was sufficient.

The cost of procedures that are considered routine and part of the rituals of an institution are often the last to be scrutinised. In this study, we considered only the financial savings made in processing the specimens in the laboratory. There was also considerable saving in effort for nursing staff who take the swabs, and laboratory staff who decide how far to characterise, identify, and establish the sensitivity of each organism cultured. The thinner sheaf of results returned to the neonatal medical staff could be considered more thoughtfully by them and filed more easily by the clerical staff.

The collation of bacteriological and clinical information from a neonatal intensive care unit is straightforward. Over a period of time, it can be used to assess changes in management critically. In this instance, we have used the monitoring system to show that the number of surface cultures performed can be reduced without detriment to patient care and with considerable saving in time, effort, and cost.

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Candida strains from neonates in a special care baby unit

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Abstract

Carriage and acquisition of *Candida* spp and *Candida albicans* biotypes were studied among 163 neonates and 90 staff in a neonatal intensive care and surgical unit during a 17 week period. Twenty one neonates carried yeasts in the mouth, rectum or groin when first sampled, and a further 25 were positive later. *C albicans* accounted for 94·7% of 431 yeast isolates from neonates but only 67·4% of 43 isolates from staff. The first isolated *C albicans* biotype persisted in 13 babies monitored longitudinally. Simultaneous colonisation with two *Candida* spp was found in 2/46 neonates and 5/33 staff. The prevalence of candida was significantly higher among babies of gestational age <28 weeks (65%) than those of higher gestational age (26%). Oral and/or crural candida infection was observed in 14 of the babies but none developed deep seated candidosis. Routine antifungal prophylaxis did not affect the frequency of yeasts among the neonates.

Deep seated forms of candida infection occur relatively infrequently in neonatal special care units[1–4] but at least one cluster of cases of disseminated candidosis has been reported in this setting[5] and an overall incidence as high as 3–4% has been estimated by some investigators.[6 7] Carriage of candida is common in neonatal units; oral and cutaneous candidosis may arise frequently and stringent antifungal antisepsis can markedly reduce the prevalence of the fungus and the incidence of candida pathologies among special care neonates.[8–11]

In most of the studies cited it has been presumed that neonatal candida infection in special care units results usually from cross infection. Phelps *et al* confirmed the occurrence of candida cross infection during an outbreak of superficial candidosis in a neonatal unit by demonstrating that a similar range of *Candida albicans* biotypes was isolated from staff and from affected babies.[12] Cross infection by *C albicans* has also been demonstrated in adult intensive care units.[13–15]

Estimates of candida carriage among neonates in special care facilities vary considerably. Phelps *et al*[12] found an overall candida colonisation rate of only 10% among 29 neonates, while higher prevalences of 19% and 27% were reported, respectively, by Hageman *et al*,[16] and Baley *et al*.[17] Lay and Russell showed that recoveries of yeasts from oral swabs increased with the duration of a baby's stay in a special care unit: 53% of the babies who had stayed for 14 days in the unit they surveyed carried yeasts.[11]

The survey by Phelps *et al* is the only one so far to involve strain typing of *C albicans* isolates as an epidemiological marker; however, this study did not involve systematic prospective sampling of the neonates and only strains from babies with pathological candidosis were typed.[12] The present study was undertaken to examine candida carriage in a prospective survey of unselected neonates in a special care unit who were sampled repeatedly during their stay on the unit. Staff in the unit were also sampled for candida carriage, and *C albicans* isolates were biotyped to determine whether the spectrum of phenotypic types in the neonates differed from that in the staff.

Patients and methods

The survey involved all 163 neonates and 90 staff present in the regional neonatal intensive care and surgical unit at Leeds General Infirmary during May to September, 1986, and a further 13 neonates selected for their extreme prematurity and sampled during the following year. The unit could accommodate a maximum of 36 babies at one time. It was divided into two sections—the special care (including intensive care) and the surgical areas. An 'open door' visiting policy existed for members of the neonate's immediate family, but other visitors were actively discouraged from attending.

The neonates in the main survey comprised 77 who were under 37 weeks' gestational age or diagnosed as suffering from respiratory distress syndrome ('premature' group), 39 admitted for surgical correction of oesophageal atresia, imperforate anus, hiatus hernia, congenital heart defects, gastroschisis, or biliary atresia ('surgical' group), and 47 with miscellaneous diagnoses, including infection, repeated cyanotic attacks, persistent jaundice, meconium aspiration, Down's syndrome, hydrops, repeated vomiting, etc ('others' group).

Anti-infection care of the neonates involved applications of an oral antiseptic solution swabbed around the inside of the mouth three to four times daily. All babies receiving antibiotic therapy also routinely received antifungal prophylaxis with miconazole gel or nystatin solution three times daily.

In the main survey, the sampling was done in two phases of eight weeks, separated by one week during which all staff who came into contact with infants were sampled. Because of the high turnover of staff and their constant movement through all areas of the unit it was

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not possible to monitor the positions of staff during the periods in which babies were sampled. For isolation of yeasts from the babies, sterile swabs premoistened in sterile 0·15 M saline were used to sample the mouth, rectal, and crural areas. These samples were taken twice a week four to five hours after the babies had received their routine drug treatments and antisepsis. Swabs were smeared on the surface of plates of Sabouraud's glucose agar (Oxoid) which were incubated for 48 hours at 37°C. Staff were sampled with oral swabs and by fingerprint impressions on Sabouraud's agar. The latter were made after staff had thoroughly washed their hands in Hibiscrub (4% chlorhexidine chlorate; ICI), as hand washing with this agent before and after handling babies was a routine procedure on the unit. The atmosphere of the unit was sampled once during each phase of the study with a Reuter Centrifugal Air Sampler, and the sterilising fluid, thermometers, zinc oxide skin cream, and 20 samples of aspirated breast milk used in the unit were also cultured for yeasts.

All samples that yielded yeast colonies were processed further for identification of the species isolated. Isolates that gave unequivocal positive results in the germ tube test for *C albicans* were identified as *C albicans*. Equivocal and negative germ tube isolates were further identified to the species level by means of API 20C AUX strips (API System, SA) and with traditional fermentation and assimilation tests[18] when necessary. Three quarters of the *C albicans* isolates from the babies and all of the isolates from staff were biotyped by the procedure described by Odds and Abbott.[19 20] This procedure involves tests for the growth of each isolate on nine agar media that detect their ability to grow at pH 1·4, production of zones of proteolysis, resistance to flucytosine, boric acid and safranine, salt tolerance, and utilisation of urea, sorbose, and citrate. Individual biotype patterns were referred to by means of three digit codes in which each digit uniquely encodes the results of three of the nine tests where a positive result is scored 1, 2, or 4, and the digit represents the total score for these tests. For example, a result of ++−−++−−+ would be encoded as 364. When multiple isolates were obtained from the same site in a patient on different occasions, a consensus biotype profile was determined by an algorithm described previously.[21] This procedure guarded against overinterpretation of differences in biotype test results as indicating strain variation: only biotypes that varied from the consensus type in more than two tests were considered as a different strain of *C albicans*.

Statistical analyses of the data were performed where appropriate by the χ^2 test or by Student's *t* test.

Results

YEAST PREVALENCE AMONG NEONATES

A total of 2386 samples were taken from 163 neonates during the main survey period. Of these, 431 (18·1%) yielded yeasts on culture; they came from 46 (28·2%) of the neonates. Twenty three (27·7%) of the 83 boys and 23 (28·8%) of the 80 girls were yeast positive (difference not significant). The carriage of yeasts among babies in the different admission categories was also statistically the same: 19/77 (24·7%) 'premature' babies, 13/39 (33·3%) 'surgical' babies, and 14/47 (29·8%) 'other' babies were yeast positive. Of the 46 yeast positive neonates, 21 were positive at the time of the first sample, and were therefore either yeast carriers at the time of their admission or may have acquired the organism on the unit before being sampled, and 25 became yeast positive in later samples and were presumed to have become yeast carriers during their stay on the unit. Crural (or perianal) pathologies and oral pathologies compatible with a candida infection were seen in 12 and two babies, respectively, during the survey (all these cases gave positive cultures). There were no instances of deep seated candida infection.

Four neonates each were colonised with *Candida* spp in oral or crural sites only and nine neonates were yeast positive only in rectal samples. Five neonates were colonised both orally and rectally but not crurally; 13 gave simultaneous positive crural and rectal cultures but remained yeast negative in oral samples, and 13 carried yeasts in all three sites sampled. No examples of oral plus crural colonisation with negative rectal cultures were found.

Only seven neonates with low birth weight (500–1000 g) and seven with a gestational age of 28 weeks or less were sampled during the main survey. Of these, four (57·1%) and five (71·4%), respectively, were positive for yeasts, as compared with 42/156 (26·9%) and 41/156 (26·3%) of babies with higher birth weights or gestational ages. Because these differences in yeast positivity approached statistical significance but the groups of extremely premature neonates was so small, an additional 13 babies with gestational age of 28 weeks or less were selected and sampled once subsequent to the main survey. Of these additional 13, eight (61·5%) carried yeast in one or two sites. Thus, the overall carriage rate of yeasts in neonates of very low gestational age (13/20; 65·0%) was significantly higher than the rate in neonates of higher gestational age (41/156; 26·3%)—$p<0·001$.

Routine antifungal prophylaxis appeared to have no significant influence on yeast carriage. There were 15 yeast positive neonates among the 52 who received miconazole (28·8%), 14 among the 42 who received nystatin (33·3%), and 17 among the 69 who received no prophylaxis (24·6%)—differences were not significant. Duration of stay in the neonatal unit also bore no significant association with yeast carriage: the mean (SD) duration of stay for babies who yielded at least one yeast positive sample was 25·5 (38·5) days as compared with 18·5 (15·7) days for babies who stayed yeast negative throughout.

SPECIES AND BIOTYPES OF YEASTS ISOLATED FROM NEONATES

C albicans was the species most frequently isolated among the neonates. It accounted for

408 (94·7%) of the 431 cultures obtained during the main survey. *C famata* was isolated once (0·2%), *C glabrata* four times (0·9%), and *C parapsilosis* 18 times (4·2%). All but two of the 46 yeast positive neonates were colonised with a single species—*C albicans* in 37 (80·4%), *C parapsilosis* in six (13·0%), and *C famata* in one. Two babies yielded samples that contained both *C albicans* and *C glabrata* in the same cultures—twice from the rectal swab in one and twice from the crural swab in the second.

A total of 306 *C albicans* isolates from 37 neonates was biotyped. The biotypes isolated are summarised in table 1. The prevalence of different biotypes was very similar for the three sites sampled: this observation, together with the longitudinal data (see below), suggests that most individual neonates acquired the same *C albicans* strain in different anatomical sites while they were in the unit. Biotype 157 was the most commonly isolated type of the 22 different types found: flucytosine resistant biotypes (first digit of the code is 4 or more) accounted for 18%, 22%, and 25% of isolates from the rectum, groin, and mouth respectively (differences not significant).

In 13 instances a total of 6–38 separate *C albicans* isolates was obtained from the same patient, permitting longitudinal monitoring of the *C albicans* types carried by the neonates (table 2). Unequivocal examples of more than one biotype occurring in the same patient were found for only 3/37 neonates (8·1%) and different biotypes were detected in a single specimen on only two occasions. Each neonate carrying yeasts in two or three of the sites sampled harboured the same biotype in the different sites. The persistence of a given strain type in an individual neonate was sometimes impressive, exceeding 30 days in seven of the 13 neonates summarised in table 2 and exceeding 60 days in three. There were no examples of babies whose *C albicans* biotype or other yeast species altered to a different one with time, as has been reported for some adult patients with haematological malignancies.[21]

Table 1 Number of occurrences of C albicans biotypes among 37 yeast positive neonates in three anatomical sites

Biotype	*Oral swabs*	*Crural swabs*	*Rectal swabs*
033	1	1	1
071	0	1	0
073	1	1	1
153	1	0	0
157	2	6	6
1 $^{5}/_{7}$ 7	1	1	1
171	0	0	1
211	1	1	1
2 $^{1}/_{5}$ 1	1	1	1
253	1	1	1
333	0	2	2
353	1	1	1
357	0	1	1
371	1	0	1
377	1	1	3
451	0	1	1
467	1	0	0
512	0	1	0
532	1	0	1
551	1	0	1
557	1	2	2
757	0	0	1

YEAST PREVALENCE AMONG STAFF

A total of 270 samples was taken from 90 staff (seven medical personnel, 78 nursing staff, and five others). Forty three samples (15·9%) from 33 staff (36·6%) gave positive cultures for yeasts. Of the 33 yeast positive staff, 28 carried yeasts in the mouth, four carried yeasts in the mouth and on the fingers, and one carried yeasts on the fingers only. There was a greater diversity of yeast species found among the staff than among the neonates, a lower prevalence of *C albicans* and a higher prevalence of samples containing more than one species. *C albicans* was isolated from the mouths of 28 staff and once from the fingers of an oral carrier, *C krusei* was isolated from two oral samples and four finger samples, *C famata* was isolated once from the mouth and fingers, and *C parapsilosis* was obtained three times from finger samples alone. *C glabrata*, *C guilliermondii*, and *Saccharomyces cerevisiae* were each isolated from single oral samples (the yeast species other than *C albicans* were coisolated with *C albicans* on three occasions). The overall prevalence of *C albicans* was therefore 67·4%, as compared with 94·7% of isolates from the neonates. Five members of staff carried two yeast species and two of these also carried more than one *C albicans* biotype.

The *C albicans* biotypes carried by the staff also showed a greater diversity than was found among the neonates. Twenty three different types were determined from 33 staff (table 3) as compared with 22 different types from 46

Table 2 Longitudinal carriage of C albicans biotypes among 13 neonates who yielded six or more yeast positive cultures

Patient No	*Oral*			*Crural*			*Rectal*		
	Biotype	*No of isolates*	*Duration (days)*	*Biotype*	*No of isolates*	*Duration (days)*	*Biotype*	*No of isolates*	*Duration (days)*
1	157	2	7	157	15	53	157	15	53
				016	1				
2	033	3	11	033	1		033	4	18
				357	2	18	357	1	
3	557	1		557	6	21	557	2	21
4				451	4	25	451	4	21
				C glabrata	2	14	400	2	21
5				157	5	14	157	6	21
6	2 $^{1}/_{5}$ 1	5	21	2 $^{1}/_{5}$ 1	14	70	2 $^{1}/_{5}$ 1	16	70
							C glabrata	2	46
7	157	1		157	3	10	157	3	10
8				333	6	14	333	6	14
9				1 $^{5}/_{7}$ 7	14	56	1 $^{5}/_{7}$ 7	14	56
10				071	9	49	071	9	49
11				377	5	39	377	8	74
12	532	10	63	512	14	63	532	14	63
13	073	8	38	073	6	28	071	11	45

Table 3 Prevalence of C albicans biotypes isolated from staff in the neonatal special care unit

No of times isolated	*Biotypes*
1	051, 075, 101, 121, 173, 253, 257, 271, 313, 333, 353, 355, 356, 457, 557, 651, 757
2	157, 251, 351, 357, 577
3	177

neonates. However, the strain types from the staff were all determined from single samples, so the apparent diversity of types may be exaggerated.[22 23] All the biotypes cultured from the neonates, or closely related strains, were represented among the staff isolates. The prevalence of flucytosine resistant isolates among the staff isolates was 20·0%—essentially the same as among the neonatal isolates.

YEASTS RECOVERED FROM ENVIRONMENTAL SOURCES

All samples from the air, fomites, and other environmental sources in the special care unit were negative for yeasts in culture.

Discussion

The overall candida colonisation rate of 28·2% among special care neonates in this study agrees well with the rate of 27% found by Baley *et al.*[17] It is higher than the 10% and 19% frequencies reported by Phelps *et al*[12] and Hageman *et al.*[16] In common with these authors we found a lower prevalence of yeast colonisation in oral samples than in samples from the groin or rectum: the overall prevalences were 13·5% (oral), 18·4% (crural), and 24·5% (rectal). We therefore agree with Phelps *et al*[12] and Hageman *et al*[16] that the lower digestive tract appears to be the first site of yeast colonisation among most neonates in a special care unit and that yeasts are readily spread from the anal region to the groins. Surveys of healthy children and adults and of hospital outpatients have usually consistently shown higher prevalences of yeasts in oral than in faecal, anal, or rectal samples[23]: we suggest that the abnormally low oral yeast prevalence in our study arises both from the frequent oral antisepsis used on the unit and the fact that most of the babies were fed via nasogastric tubes. Other surveys of neonates receiving special care have found higher prevalences of yeasts in the mouth than in samples from other sites[12 24] and Lay and Russell[11] isolated *Candida* spp or other yeasts from 53% of the mouths of babies who remained in a special care unit for 14 days.

The considerable variations between the different surveys strongly suggest that rates of candida carriage may be altered by the conditions that prevail in a special care unit, management protocols that may enhance or reduce transmission of candida, and the nature and intensity of routine anti-infective hygiene measures employed: as all the surveys used swabs as sampling devices the differences are unlikely to be attributable to methodological variations. The composition of the patient populations in the different studies is also likely to influence the apparent carriage rates: for example, study populations with a high proportion of patients of low birth weight might be expected to have a higher candida prevalence, as we found a much higher rate of yeast colonisation among babies of very low gestational age. However, 75% of the babies studied by Baley *et al*[17] had birth weights <1500 g, yet their candida carriage rate was not higher than ours. Thus, differences between studies probably reflect complex differences between units and their protocols more than any simple single factor.

One factor that should, in theory, alter rates of candida carriage is the prophylactic use of antifungal drugs. However, in the present study neither miconazole gel nor nystatin suspension given orally significantly affected the candida carriage rates. The quantities of these drugs used (0·2 ml in each case) may have been too small to affect candida colonisation. Harris *et al*, who reduced oral candida carriage among their neonates by 50% with nystatin, used five times this dosage.[9]

The *Candida* spp isolated from the neonates in our study were qualitatively very similar to those reported in similar settings by others. Hageman *et al*[16] found *C parapsilosis* in 38% of the neonates they studied and *C glabrata* in 4%. Baley *et al*[17] found *C albicans* in 62%, *C parapsilosis* in 18%, *C tropicalis* in 8%, and *Trichosporon pullulans* in 3%. However, the overall prevalence of *C albicans* in our study (95%) was much higher than in either of the others cited, and much higher than the 67% prevalence of *C albicans* isolated from the staff (though this may be at least partly determined by the different sites sampled in the two groups). The particularly high prevalence of *C albicans* in the neonates studied gives some cause for concern. In his extensive review of epidemiological publications on candidosis, Odds calculated that *C albicans* accounted for 70% of oral yeast isolates, 51% of anorectal tract isolates, and it was rarely recovered from skin samples except in patients with cutaneous candida infections.[23] It seems likely that this most pathogenic of the *Candida* species was selected for in the neonatal population, placing them at heightened risk of candida based pathology.

The spectra of *C albicans* biotypes found among staff and patients were broadly similar. Type 157 was previously associated with an outbreak of disseminated candidosis in a hospital intensive care unit[13] and with disseminated candidosis in heroin addicts.[25] As it was also the most prevalent biotype among the neonates (table 1), our findings confirm that this particular biotype may have a higher ability than some other strains to colonise patients. The strain types 153 and 1 $^{5}/_{7}$ 7 are closely related to type 157: considered together, these strains were involved in seven of the 12 instances of cutaneous (crural) candida associated pathology and one of the two instances of oral thrush diagnosed during this study. Coincidentally and anecdotally, two cases of disseminated candidosis that were diagnosed in our unit before the present study was undertaken were both caused by *C albicans* biotype 157.

Our study was done before the advent of methods suitable for DNA typing of *C albicans*[15 26 27] so that only phenotypic differentiation was done. It will be interesting in the future to determine whether DNA typing reveals similar associations between particular *C albicans* genotypes and neonatal candida carriage and infection.

It was not possible to monitor possible routes of transmission of candida between individual staff and patients. Nor were we able to sample parental yeast flora for administrative and ethical reasons. However, the general similarities between the *C albicans* biotypes isolated from staff in the unit and the absence of *C albicans* in samples from the environment strongly implicate person to person contact as the major route of transmission of candida in the unit. The stability of *Candida* spp and biotypes isolated longitudinally from babies in the neonatal unit suggests that, even if the initial colonisation event amounts to cross infection, the colonising strain remains immune from subsequent replacement by other strains or species in the unit. This situation differs from that seen in a longitudinal study of candida carriage in patients with haematological malignancy, where changes in candida flora were found in oral and stool samples, particularly in patients monitored for longer than 14 days.[21] We agree with Phelps *et al*[12] that transmission between staff and neonates is, in the circumstances, the most likely means for propagation and dissemination of potentially pathogenic yeasts within a neonatal special care unit.

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Enterobacteriaceae and neonatal necrotising enterocolitis

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Abstract

A comparative study of bowel colonisation and incidence of necrotising enterocolitis in neonates admitted to an intensive care unit is reported. Neonates of less than 33 weeks gestational age requiring mechanical ventilation for respiratory distress syndrome were randomised during the first week of life to receive either vancomycin and aztreonam or vancomycin and gentamicin for episodes of suspected sepsis after the first week of life. A higher proportion of neonates who received vancomycin and gentamicin had faecal colonisation with enterobacteriaceae at the end of the second, third, and fourth weeks of life. Treatment with vancomycin and aztreonam was associated with a rapid quantitative reduction in faecal colonisation with enterobacteriaceae, whereas there was no quantitative reduction in colonisation with enterobacteriaceae associated with treatment with vancomycin and gentamicin. There were no differences between the two groups in faecal colonisation with anaerobes, *Enterococcus* sp, *Staphylococcus* sp, or yeasts. Six (14·6%) of 41 who received vancomycin and gentamicin compared with 0 of 40 who received vancomycin and aztreonam subsequently developed necrotising enterocolitis.

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Neonatal necrotising enterocolitis is the most common abdominal emergency in neonatal intensive care units. Clustering of cases of necrotising enterocolitis in time and place has led to the hypothesis that it has an infective aetiology. Many studies have suggested a link between enterobacteriaceae and necrotising enterocolitis.[1–5] In a previous study we reported changes in the faecal flora preceding the clinical onset of necrotising enterocolitis by up to 72 hours and these changes included a quantitative increase in enterobacteriaceae.[6]

Aztreonam has been shown to be comparable in efficacy to aminoglycosides for the treatment of Gram negative infections in adults[7] and neonates.[8] Preliminary studies in this neonatal unit suggested that treatment of neonates with intravenous aztreonam reduced bowel colonisation with enterobacteriaceae.

In this study we compared the changes in bowel flora and incidence of necrotising enterocolitis in neonates treated with vancomycin and gentamicin or vancomycin and aztreonam for episodes of suspected sepsis after the first week of life.

Patients and methods

Neonates of less than 33 week's gestational age admitted to the Peter Congdon Regional Neonatal Unit in Leeds between February 1989 and April 1990 were randomised during the first week of life to receive intravenous vancomycin (22 mg/kg every 12 hours) with gentamicin (3 mg/kg every 12 hours) or vancomycin with aztreonam (15 mg/kg every 12 hours) for episodes of suspected bacterial infection occurring after the first week of life. The diagnosis of suspected infection was made clinically and the clinical signs included apnoea, bradycardia, metabolic acidosis, hypotension, unstable temperature, and poor peripheral perfusion. Antibiotic treatment after the first week of life was modified if indicated by laboratory results or the clinical condition of the neonate. Neonates with suspected necrotising enterocolitis were treated with benzylpenicillin or ampicillin, gentamicin, and metronidazole.

Samples of faeces were collected each day (when available) from all neonates during the first month of postnatal life, weighed and stored at −70°C in glycerol citrate broths as previously described.[6] Faecal bacteriology was performed within six months of sample storage. Samples were thawed at room temperature and vial contents serially diluted 10-fold in brain heart infusion broth (Oxoid CM225). An aliquot of 100 μl of each dilution was spread onto a range of selective and non-selective media,[6] which were incubated for seven days. Aztreonam concentrations were determined in stored samples using a plate diffusion assay. Gentamicin was assayed using both a plate assay[9] and an immunoassay method (Abbot TDx). Minimum inhibitory concentrations (MIC) of antibiotics for bacterial isolates were determined using a plate dilution method.[9] Resistance was defined by an MIC exceeding 1 mg/l. The proportions of neonates at 7, 14, 21, and 28 days of postnatal age colonised by enterobacteriaceae, enterococci, yeasts, anaerobes, *Staphylococcus aureus*, and coagulase negative staphylococci were determined by examining the sample collected from each neonate nearest to, but within 72 hours, of 7, 14, 21, and 28 days of postnatal age.

The diagnosis of necrotising enterocolitis was suspected if an infant developed illness associated with specific signs of gastrointestinal dysfunction including abdominal distension, blood in the stool, gastric retention, and abdominal wall erythema. A plain radiograph was taken in all infants with suspected necrotising enterocolitis. The radiographs were reviewed by a paediatric radiologist unaware of the clinical signs. Definite necrotising enterocolitis was diagnosed if there were radiological signs of intramural or intrahepatic gas, otherwise the episodes were considered as possible necrotising enterocolitis.

Local ethics committee approval was obtained for this study.

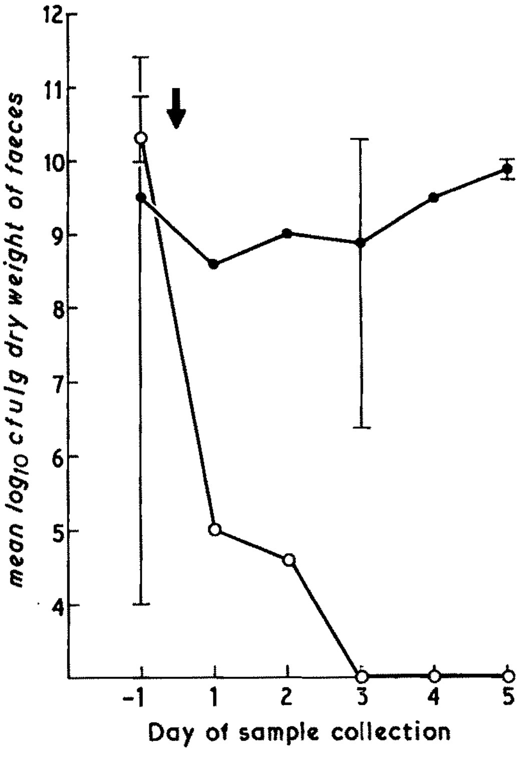
Statistical analysis was carried out using logistic regression with the EGRET software package. Two sided significance tests were used.

Results

Over the 15 month study period 143 neonates were randomised to receive vancomycin and gentamicin or vancomycin and aztreonam for episodes of suspected sepsis after the first week of life. Forty one neonates received vancomycin and gentamicin and 40 received vancomycin and aztreonam after the first week of life. The median duration of antibiotic treatment in the two groups was five days. The clinical features of the two groups are shown in table 1. The two groups of neonates had similar clinical features during the first week of life. Two neonates to whom vancomycin and aztreonam were administered died before enteral feeding was started. The median postnatal age at which enteral feeding was started was 9 days in the group which received vancomycin and gentamicin and 10 days in the group which received vancomycin and aztreonam. If tolerated, then feed volumes were gradually increased from 10 ml/kg/24 hours to full feed volumes over seven days. Fourteen (35%) of the group which received vancomycin and aztreonam compared with 15 (36·6%) of the group which received vancomycin and gentamicin were partially or fully enterally fed with maternal breast milk.

There were eight episodes (involving eight neonates) in the group which received vancomycin and aztreonam and 11 episodes (involving 11 neonates) in the group which received vancomycin and gentamicin where enterobacteriaceae were present at the start of treatment and in which treatment was continued for more than 72 hours. Enterobacteriaceae were present at the end of the treatment in none of the eight episodes in the group that received vancomycin and aztreonam and in all of the 11 episodes in the group that received vancomycin and gentamicin. None of the strains of enterobacteriaceae present before or after treatment were resistant to aztreonam or gentamicin (MIC more than 1 mg/l). There were seven episodes in the group which received vancomycin and aztreonam and eight episodes in the group which received vancomycin and gentamicin for which at least three samples were available within the five day period after introduction of antibiotic treatment. Quantitative studies of enterobacteriaceae showed that there was a rapid fall in the mean $\log_{10}$ colony forming units (cfu)/g dry weight associated with administration of vancomycin and aztreonam and no fall in numbers in the group receiving vancomycin and gentamicin (figure). In the group receiving vancomycin and aztreonam, inhibitory concentrations of aztreonam were detected in faecal samples. Inhibitory concentrations of gentamicin were not detected in the group receiving vancomycin and gentamicin.

The proportion of neonates in each group for whom samples were available at each time were similar. The proportion of neonates at 14, 21, and 28 days from whom enterobacteriaceae were isolated was significantly higher in the group which received vancomycin and gentamicin than in the group which received vancomycin and aztreonam (table 2). There were no



Quantitative changes in enterobacteriaceae in faecal flora with intravenous vancomycin and aztreonam or gentamicin; ○=vancomycin and aztreonam ●=vancomycin and gentamicin. The arrow indicates the start of intravenous antibiotics and vertical bars the SD.

Table 1 Clinical features of neonates receiving vancomycin and aztreonam or vancomycin and gentamicin

	Vancomycin and aztreonam (n=40)	*Vancomycin and gentamicin (n=41)*
Median gestational age in weeks (range)	27 (24–32)	28 (24–32)
Median birth weight (g)	1040	910
<1000 g (%)	47·5	53·7
Umbilical artery catheter (%)	72·5	63·4
Intraventricular haemorrhage diagnosed by ultrasound (%)	40·0	29·3
Pneumothorax (%)	12·5	7·3
Treatment for patent ductus (%)	22·5	36·6
Outborn (%)	37·5	43·9
Bacteraemia in first week (%)	5·0	2·4
IPPV >24 hours (%)	92·5	80·5
Apgar score <5, at 5 minutes or IPPV more than 4 minutes from birth (%)	60·0	70·7
Hypoglycaemia (%)*	7·5	7·3

IPPV, intermittent positive pressure ventilation.
*Glucose concentration <1·2 mmol/l.

Table 2 Percentage with enterobacteriaceae isolated at each postnatal age

Postnatal age (weeks)	*Group*	*No of samples*	*% With enterobacteriaceae*
1	VA	31	19·4
	VG	35	34·3
2	VA	31	25·8
	VG	35	60·0
3	VA	30	30·0
	VG	29	75·9
4	VA	18	50·0
	VG	23	87·0

VA refers to neonates who received vancomycin and aztreonam and VG to neonates who received vancomycin and gentamicin. The differences in percentage with enterobacteriaceae at 2, 3, and 4 weeks of postnatal age: χ^2 at 2 weeks=7·8 ($p<0·01$), at 3 weeks=12·4, and at 4 weeks=6·7.

Table 3 Outcome of neonates treated with vancomycin and aztreonam and vancomycin and gentamicin

	Group	
	Vancomycin and aztreonam (n=40)	*Vancomycin and gentamicin (n=41)*
No who died	6	4
No with necrotising enterocolitis		
Definite	0	6
Possible	14	13
No with chronic lung disease	9	5
Median hospital stay (days)	40	43

differences in the proportions of samples from the two groups from which anaerobes, enterococci, yeasts, or staphylococci were isolated at each postnatal age.

The proportion of neonates who died before discharge from hospital or developed chronic lung disease and the median duration of hospital stay were similar in the two groups (see table 3). A larger proportion of neonates in the group which received vancomycin and gentamicin (six of 41) developed definite necrotising enterocolitis compared with the group which received vancomycin and aztreonam (six of 41 *v* 0 of 40; p 0·028; Fisher's exact test). To be sure that this difference was not attributable to differences between the two groups other than antibiotic treatment, the effect that each of the clinical characteristics had on outcome was examined in a logistic regression model. The only variable to have a significant effect on the risk of necrotising enterocolitis independently of antibiotic group was the presence of an umbilical artery catheter; an umbilical artery catheter was associated with a reduced risk of necrotising enterocolitis.

All of those that developed definite necrotising enterocolitis had received vancomycin and gentamicin preceding the onset of clinical signs of necrotising enterocolitis. A similar proportion of neonates in the two groups developed possible necrotising enterocolitis. Faecal samples were available from the 48 hour period preceding the onset of five of the six episodes of definite necrotising enterocolitis. Enterobacteriaceae were present preceding all of these five episodes.

Discussion

Intravenously administered antibiotics may have a profound influence on the pattern of development of the gastrointestinal flora of premature neonates.[10] In this study we have shown a reduction in bowel colonisation with enterobacteriaceae associated with the intravenous administration of aztreonam but not gentamicin. The majority of premature neonates in intensive care units receive antibiotics. The clinical signs of bacterial infection are nonspecific, so that many receive antibiotics in the absence of laboratory or radiological evidence of infection. The pattern of antibiotic usage varies considerably between neonatal units,[11] yet there have been few studies comparing the impact of different regimens on the development of the neonatal faecal flora.

In this study we have presented evidence suggesting that intravenously administered aztreonam and vancomycin by comparison with gentamicin and vancomycin reduces faecal colonisation with enterobacteriaceae. Although both aztreonam and gentamicin are excreted in the bile, the peak serum concentrations of aztreonam are considerably higher than those of gentamicin and this may explain the differences in faecal antimicrobial activity. The antimicrobial activity of biliary excreted gentamicin may also have been reduced by anaerobic conditions, low intraluminal pH, and the presence of divalent cations such as calcium ions. No attempt was made to separate the two groups of neonates within the intensive care unit, so that cross colonisation was not prevented. Prevention of cross colonisation might have led to greater differences in the patterns of bacterial colonisation between the two groups.

If enterobacteriaceae are involved in the pathological process leading to necrotising enterocolitis then its difference in incidence between the two groups could be explained by modification of the bowel flora before or soon after the onset of that pathological process. However, other explanations cannot be excluded such as direct effects of antibiotics on the bowel. Past attempts to prevent necrotising enterocolitis through modification of the gastrointestinal flora by orally administered aminoglycosides have not produced conclusive results,[12-14] although the small number of neonates included and the rapid selection of aminoglycoside resistant enterobacteriaceae after the use of oral aminoglycosides[12] may have contributed to the inconclusive nature of these studies.

This study certainly does not refute the hypothesis that colonisation of the bowel of premature neonates with enterobacteriaceae contributes to the pathogenesis of neonatal necrotising enterocolitis. It suggests that the specific antibiotics used for the intravenous treatment of neonates with suspected infection may influence the risk of the subsequent development of necrotising enterocolitis.

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Pharmacokinetics and antibacterial activity of daily gentamicin

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Abstract

Twenty full term neonates with suspected bacterial infection were randomly assigned to a once daily or a twice daily dosage regimen with gentamicin (4 mg/kg/day). Concomitantly all patients were treated with ampicillin (200 mg/kg/day). The gentamicin concentration time curves were analysed by an open two compartment model under steady state conditions on day 4 of treatment. The mean theoretical maximum serum concentration in the group taking gentamicin once daily (10·9 μg/ml) was significantly higher than in the group taking it twice daily (7·4 μg/ml). Potentially toxic serum concentrations were never reached. Mean trough concentrations were comparable in both groups (once daily 0·8 μg/ml; twice daily 1·0 μg/ml). Urinary alanine aminopeptidase excretion increased during and even two days after end of treatment in both groups without any significant differences.

The results of the dynamic in vitro model revealed that both dosage schedules showed comparable bactericidal effects on pathogens inhibited by low concentrations of gentamicin like *Escherichia coli* and *Staphylococcus aureus*. However the once daily regimen was significantly superior in isolates with high minimal inhibitory concentrations.

The combination of gentamicin, as a representative of aminoglycoside antibiotics, with β lactam antibiotics is widely used. It has been proved as an effective antibiotic strategy in neonates with suspected or documented bacterial infection. Gentamicin, like all other aminoglycosides, exhibits a narrow range between toxic and therapeutic dosages. It is generally accepted that peak concentrations >4 μg/ml are necessary for antibacterial efficiency and that trough concentrations of >2 μg/ml are a risk factor for nephrotoxicity and ototoxicity.[1-3] It has been shown that the bactericidal activity of aminoglycosides is dependent on plasma concentrations and that higher peak concentrations are associated with improved therapeutic response in life threatening bacterial infection.[1 2]

Furthermore, aminoglycosides exhibit a postantibiotic effect that correlates with the extent of peak concentration above the minimal inhibitory concentration for the infecting organism.[4] These data and results of preliminary studies concerning aminoglycoside associated nephrotoxicity and ototoxicity provide support for a once daily aminoglycoside dosing schedule.[1 5 6] Because elimination half lifes of aminoglycosides are longer in neonates than in older children and adults the daily single dose regimen might be a less toxic and more effective approach in this age group.[6-10]

The aims of this study were the evaluation of pharmacokinetic profiles of gentamicin in neonates in once and twice daily dosage regimens, the determination of antibacterial properties of these profiles in a dynamic in vitro model, and finally the influence of the dosing regimens on urinary excretion of alanine aminopeptidase. Alanine aminopeptidase is a brush border associated enzyme of the proximal renal tubules and acts as a marker of preclinical nephrotoxicity.[5 11]

Patients and methods

Twenty neonates with pneumonia (n=7), meconium aspiration (n=2), suspected bacterial infection indicated by C reactive protein concentration >8 mg/l (n=4) and premature rupture of membranes >36 hours before delivery (n=7) were studied. They were included in the study on the first to third postnatal day after obtaining informed parental consent. Patients with a gestational age <37 weeks, Apgar scores ≤4 (1 min) and ≤6 (5 min), birth weight <2500 g, serum creatinine concentrations >85 μmol/l, and those who required diuretics during the course of treatment as well as those who were exposed to aminoglycosides prenatally were excluded from the study.

The babies were randomly assigned to a once daily (GM I; 4 mg/kg) and twice daily (GM II; 2×2 mg/kg) dosage regimen with gentamicin. All patients were concomitantly treated with ampicillin (200 mg/kg/day). Characteristics of the study population are shown in table 1.

Gentamicin was administered over 30 minutes using a syringe pump. The pharmacokinetic profile of gentamicin in serum was determined on the fourth day of treatment. Blood samples (0·4 ml) were obtained from a venous catheter, 1, 4, 6, 12, and 24 (GM I only) hours after starting the infusion. The serum concentration of gentamicin was measured with a fluorescence

Table 1 Characteristics of study population

	GM I	*GM II*
No of patients	10	10
Male/female	3/7	5/5
Gestational age (weeks)	39·5 (1·4)	40·3 (0·8)
Age (days)	1·3 (1·1)	0·7 (0·7)
Weight (kg)	3·3 (0·6)	3·8 (0·6)
Serum creatinine (μmol/l)	67 (12)	61 (14)
Duration of treatment (days)	9 (1·7)	8 (1·7)

Results are mean (SD).

polarisation immunoassay (TD_x-System, Abbott) immediately after sample collection.

Serum concentration time curves of gentamicin were fitted using the Rotating Iterative Procedure program with the assumption of an open two compartment model.[12] Areas under the concentration time profiles (AUC) for gentamicin concentrations >4 µg/ml were calculated by the trapezoidal method. Pharmacokinetic parameters such as theoretical maximal concentrations and AUC for 24 hours derived from curve fitting to a two compartment model.

Urine was sampled for three hours between 6 am and 9 am using a urine collection bag on the second, fourth, and sixth day of treatment, and two days after gentamicin treatment was discontinued. Traces of sodium azide as a preservative were added to urine samples which were stored at 4°C for a maximum of 48 hours. After gel filtration (Sephadex column G25 PD10) the activity of alanine aminopeptidase was determined photometrically (405 nm) using L-alanine-p-nitroanilide as the substrate with a method described by Mondorf *et al.*[11] Urine concentrations of creatinine were assayed with a modified method described by Popper *et al.*[13] Alanine aminopeptidase activities were related to urinary creatinine concentrations and were corrected for body surface areas.

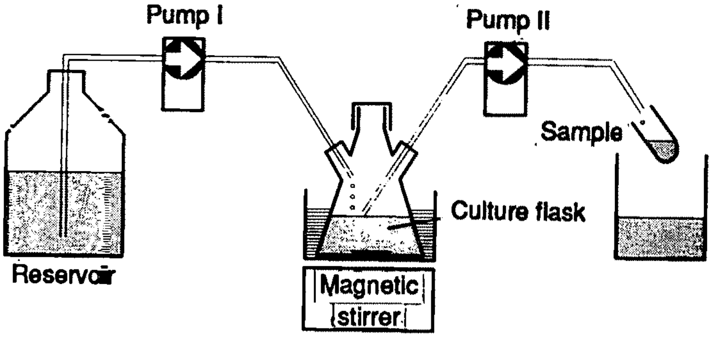

Figure 1 Schematic drawing of the applied in vitro model (for explanation of concentration adjustment see text). Pump II was run at about five times the flow rate of pump I, thus drawing filtered air into the culture flask to avoid anaerobic conditions. Volume constancy in the culture flask was provided by setting the outflow tube to a fixed level.

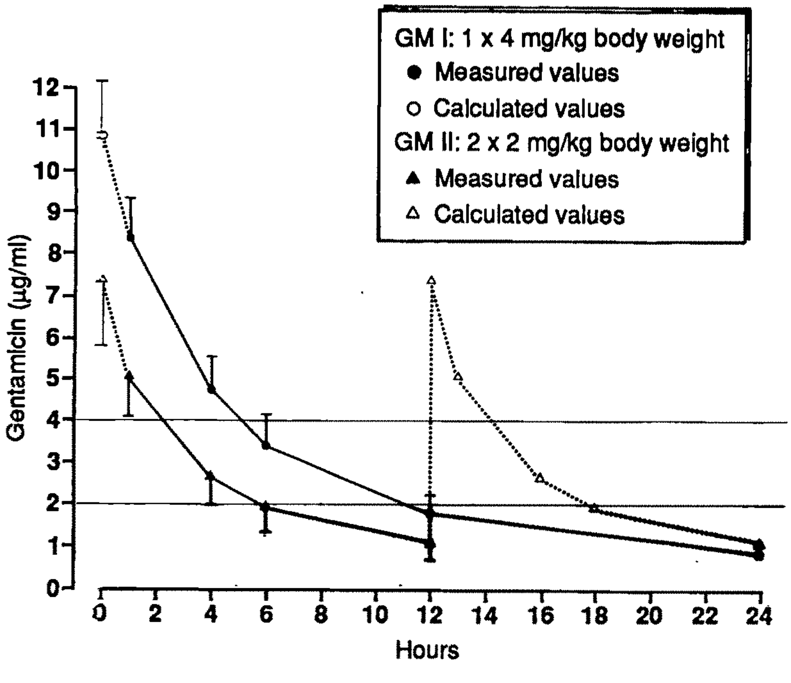

Figure 2 Mean (SD) serum concentration time curves of gentamicin.

Statistical analysis was performed by Fisher's permutation test.

IN VITRO MODEL

The antibacterial activity of the mean serum gentamicin concentrations obtained with both dosing regimens was analysed in an in vitro model according to Grasso *et al* (fig 1).[14] Due to the non-log linear serum concentration time curve gentamicin kinetics in the culture bottle of the in vitro model were simulated by an hourly adjustment of the pumping velocity. The exact necessary adjustment was determined empirically in provisional experiments. Gentamicin concentrations were determined by microbioassay using *Bacillus subtilis* ATCC 6633 as indicator strain at the time points indicated.

Growth medium in all experiments was standard I broth (E Merck). Test strains were the standard strains *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC, 25933, *Pseudomonas aeruginosa* ATCC 27853, and the clinical isolates *Listeria monocytogenes* OM 189 (gentamicin minimal inhibitory concentration 2 µg/ml) and *Enterococcus faecalis* OM 25 (gentamicin minimal inhibitory concentration 4 µg/ml). The inoculum size was set to approximately 1×10^6 colony forming units (cfu) by diluting a static over night culture 1: 500 for *E coli*, *S aureus*, and *P aeruginosa* and 1:250 for *E faecalis*, and *L monocytogenes*.

Results

PHARMACOKINETIC DATA

The theoretical concentration (C_o) of gentamicin in serum derives from extrapolation of the concentration time plot to time zero (figs 2 and 3). Values for C_0 ranged from 8·5 to 13·0 µg/ml in group GM I and from 5·2 to 10·1 µg/ml in group GM II. The measured peak serum concentraion (C_{max}) never exceeded the potentially

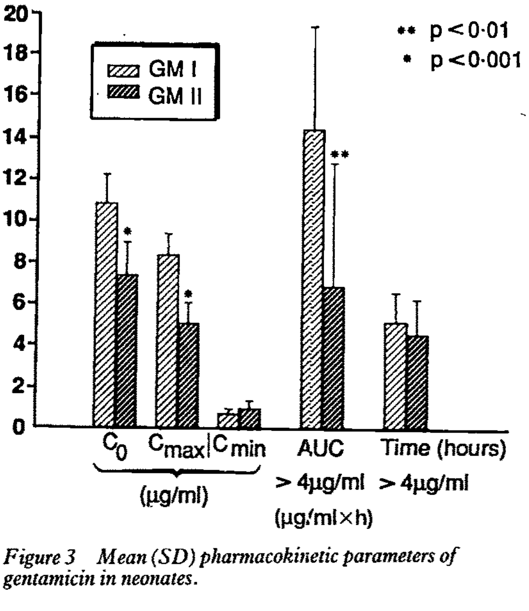

Figure 3 Mean (SD) pharmacokinetic parameters of gentamicin in neonates.

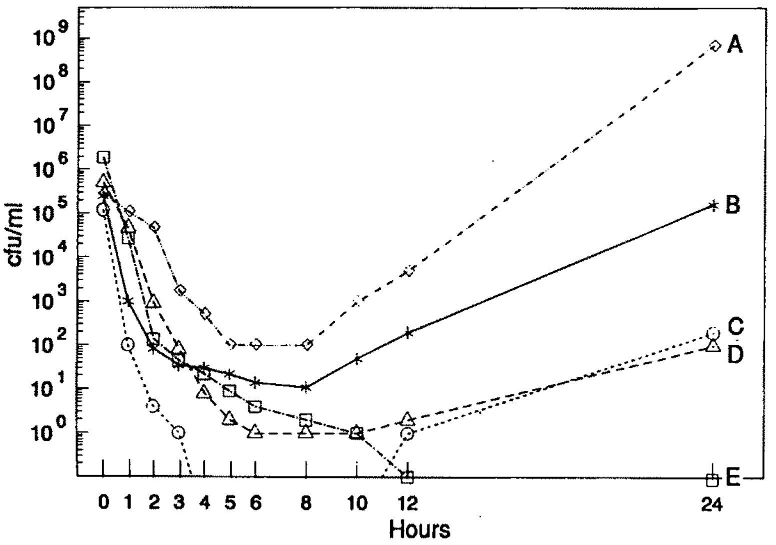

Figure 4 Bactericidal activity of gentamicin in the in vitro model obtained after simulating GM I pharmacokinetics. (A) Enterococcus faecalis OM 25, (B) Pseudomonas aeruginosa, ATCC 27 853, (C) Escherichia coli ATCC 25 922, (D) Staphylococcus aureus ATCC 25 923, (E) Listeria monocytogenes OM 189.

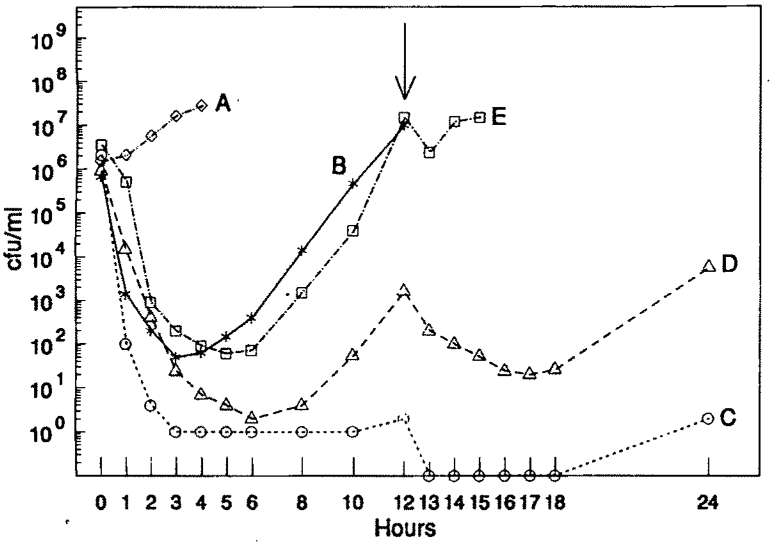

Figure 5 Bactericidal activity of gentamicin in the in vitro model obtained after simulating GM II pharmacokinetics. (A) Enterococcus faecalis OM 25, (B) Pseudomonas aeruginosa, ATCC 27 853, (C) Escherichia coli ATCC 25 922, (D) Staphylococcus aureus ATCC 25 923, (E) Listeria monocytogenes OM 189. Arrow indicates second dose.

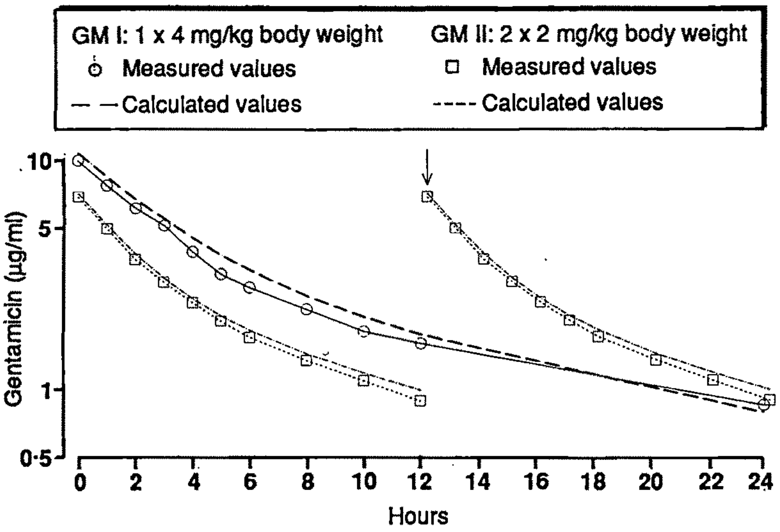

Figure 6 Comparison of gentamicin concentrations calculated from the mean pharmacokinetic parameters obtained from the patients and the concentrations determined in the in vitro mode. Arrow indicates second dose.

toxic concentration of 12 µg/ml (figs 2 and 3). They ranged from 7·0 to 9·9 µg/ml and from 4·1 to 7·7 µg/ml in group GM I and GM II, respectively.

Both C_0 and C_{max} were significantly higher in the once daily group whereas the trough concentrations (C_{min}), which ranged from 0·5–1·2 µg/ml (mean (SD) GM I: 0·8 (0·2) µg/ml) and from 0·5–1·7 µg/ml (GM II: 1·0 (0·4) µg/ml), showed no significant differences ($p>0·1$) between the dosage schedules. The areas under the concentration time curves (AUC_{0-24}) were in comparable ranges in both treatment groups (mean (SD) GM I: 63·27 (10·6) µg/ml×h; GM II: 50·90 (8·5) µg/ml×h; $p>0·02$). AUC for gentamicin concentrations >4 µg/ml ranged from 9·7 to 24·7 µg/ml×h (mean (SD) GM I: 14·5 (5·0) µg/ml×h) and from 1·3 to 22·8 µg/ml×h (GM II: 6·9 (6·0) µg/ml×h). They were significantly higher in group GM I ($p<0·01$). The time periods/24 hours in which the concentrations of gentamicin exceeded 4 µg/ml were in comparable ranges in both groups (fig 3).

ALANINE AMINOPEPTIDASE URINARY EXCRETION

Alanine aminopeptidase excretion increased in both treatment groups in the same pattern during and even after discontinuation of gentamicin therapy (table 2). Significant differences were not detectable between the groups at any time.

IN VITRO MODEL

Figures 4 and 5 show the results of the in vitro model experiments obtained after simulating the mean gentamicin serum concentration curves for GM I and GM II. The initial gentamicin concentrations were set to 10·7 µg/ml in the GM I model and to 7·2 µg/ml in the GM II model. In the GM I model gentamicin concentrations decreased slightly faster than calculated from the pharmacokinetic data, whereas in the GM II model there was a good correlation to the calculated values (fig 6).

In the GM I model all strains tested responded to the high initial concentrations of gentamicin by a rapid decrease of viable cell counts (fig 4). Significant regrowth was seen in the cultures of *E faecalis*, *P aeruginosa*, and *E coli* starting after eight to 10 hours. For *P aeruginosa* and *E coli* the 24 hour cfu counts remained below the value for time zero.

In the GM II model (fig 6) all strains but *E faecalis* were rapidly decreased in cfu counts. Significant regrowth started for *L monocytogenes*, *S aureus*, and *P aeruginosa* after four to six hours and the value for time zero was reached within

Table 2 Mean (SD) urinary alanine aminopeptidase excretion during and after treatment with gentamicin. Alanine aminopeptidase activities were related to urinary creatinine concentrations and were corrected for body surface areas (U/mmol/m²)

	GM I	*GM II*
During treatment		
Day 2	27·8 (23·6)	29·1 (16·6)
Day 4	46·1 (34·1)	35·7 (22·2)
Day 6	47·1 (30·6)	44·1 (13·8)
After treatment		
Day 2	50·5 (14·6)	58·7 (23·9)

12 hours (before the second dosing). The second dose added to the culture resulted in a decrease of cfu counts for *S aureus* with regrowth again starting after about six hours. On *L monocytogenes* the second dose had a small influence only and no reduction in growth was seen for the *P aeruginosa* strain.

Discussion

Pharmacokinetic data of gentamicin indicate that elimination half lives are longer in neonates especially in preterm infants compared with older children.[7–10] Routine drug monitoring in neonates receiving intravenous gentamicin on a twice daily dosage schedule reveals that especially in preterm infants trough concentrations often exceed the potential toxic concentrations of >2 μg/ml which are not accompanied by raised peak serum concentrations.[15] These data lend support for the recommendation to increase the dosing interval from 12 to 18–24 hours.[19 16 17] All our patients show gentamicin serum concentrations in the therapeutic range; potentially toxic trough and peak (>12 μg/ml) concentrations[18] are not recorded under steady state conditions in this study. Determinants which might alter gentamicin elimination such as asphyxia, impaired renal function, and concomitant diuretic treatment are excluded.[10 19]

Recent studies have shown that therapeutic efficacy of aminoglycosides depends on peak concentrations and the AUC above the minimal inhibitory concentration of the infecting organism rather than duration of time serum concentrations exceed the minimal inhibitory concentration.[2 20] The results obtained with the in vitro model of Grasso *et al* strongly underline that high peak concentrations of gentamicin are the main determinant for antibacterial activity.[14] Most clearly this can be seen with the *E faecalis* strain, which is strongly reduced in the GM I model and uninfluenced in the GM II model. In both treatment groups the duration of time for gentamicin concentrations >4 μg/ml and the total AUC are in comparable ranges whereas the AUC above the level of 4 μg/ml is significantly higher in the once daily dosing group.

Although a postantibiotic effect is demonstrated for aminoglycosides, a reduction of dosing frequency might bear the risk of bacterial regrowth, especially if the dosing interval is longer than the duration of time of serum concentrations above the minimal inhibitory concentration plus the postantibiotic effect. This risk factor can obviously be balanced by the observation that the postantibiotic effect of gentamicin and its duration correlates with peak concentrations in serum and AUC above the minimal inhibitory concentration of the infecting organism and the fact that the elimination half life of gentamicin is longer in neonates than in older children.[4]

The mechanism of drug induced renal toxicity is the same for all aminoglycosides. After glomerular filtration a small fraction of aminoglycosides is reabsorbed in the proximal renal tubular cells by endocytosis.[21] Aminoglycoside nephrotoxicity is caused by inhibition of lysosomal phospholipase and sphingomyelinase of the proximal tubular cells resulting in phospholipidosis of the lysosomes and formation of myeloid bodies.[1 21 22] This leads to the loss of membrane integrity and finally to tubular necrosis.[23] The risk of aminoglycoside induced toxicity is a function of cortical aminoglycoside concentration.[1] As cortical uptake of aminoglycoside shows at least for gentamicin a pattern of saturable kinetics it is evident that different dosing regimens can affect the cortical accumulation of gentamicin.[1 21] This assumption is validated by the results of a study where patients received the same dose of gentamicin either as a continuous infusion or as a single injection before nephrectomy.[24] Renal gentamicin concentrations were significantly lower in the latter group.

After continuous infusion of gentamicin significantly lower creatinine clearance and excretion of β_2-microglobulin are found in neonates than after a twice daily dose regimen.[25]

The excretion of alanine aminopeptidase a brush border associated enzyme of the proximal renal tubules into the urine is a sensitive parameter of preclinical gentamicin nephrotoxicity.[15 11 26] Gentamicin induced enzymuria is lower in neonates than in adults; this is in accordance with clinical studies that renal toxicity is less frequent in newborns.[7 27] The latter can be explained by a lower rate of renal gentamicin accumulation in the neonate.[7] The patterns of alanine aminopeptidase excretion are similar in both treatment groups; this is in contrast to a study in healthy volunteers where more pronounced enzymuria was recorded on a twice daily dosage regimen.[5]

Contrary to nephrotoxicity the mechanism of ototoxicity of aminoglycosides remains to be determined. Several risk factors such as duration of treatment, total dose, the AUC, and impaired renal function are identified.

Another study reported that patients with auditory toxicity who underwent treatment for a longer period were more likely to be bacteraemic and had, on average, a higher temperature.[28] Experimental studies give some evidence that less frequent dosage regimens cause less ototoxicity.[1] Summarising the recent data on aminoglycoside toxicity there is some evidence that raised trough rather than peak serum concentrations are the main determinant of both nephrotoxicity and ototoxicity.

In conclusion, the results of this study indicate that the once daily dosage regimen of gentamicin in term infants guarantees peak serum concentrations above the minimal inhibitory concentration of bacteria, which are relevant in the neonatal period, and trough concentrations below the potentially toxic concentration of 2 μg/ml. From the results of the dynamic in vitro model it can be concluded that the single daily dose administration is superior to the twice a day regimen. As alanine aminopeptidase release from the proximal tubular cells into the urine as a sensitive marker of preclinical renal toxicity is similar in both dosing schedules, an increased risk for nephrotoxicity is unlikely to occur on a once daily regimen. Whether this approach of larger less frequent doses provides similar advantages in preterm infants where dosage intervals are already considerably extended remains to be investigated.

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Cyclical fluctuations in cerebral blood volume

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Abstract

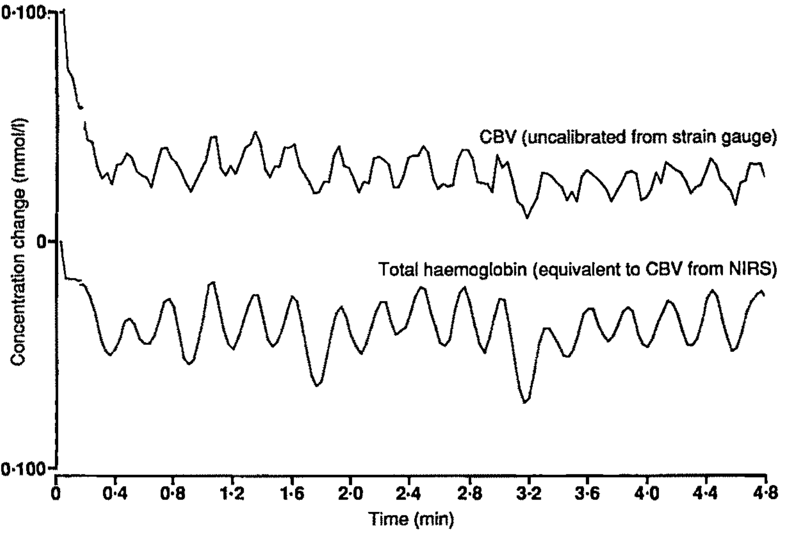
Cyclical fluctuations of cerebral blood flow velocity have been reported previously using Doppler ultrasound. The same phenomena was detected during investigations of changes in cerebral blood volume using near infrared spectroscopy. Rhythmic fluctuations of cerebral blood volume at a frequency of 3·5 cycles/minute is reported here.

Anthony *et al* have recently reported cyclical variability (1·5–5 cycles/minute) in cerebral blood flow velocity (CBFV) as measured by pulsed wave Doppler ultrasound in both sick and healthy infants.[1] This is thought to represent cycling of cerebral blood flow and has been previously documented using similar techniques.[2] This phenomenon appears to be peculiar to the neonate, both preterm and full term, and has not been reported in adults.[1] It has been suggested that rhythmical changes in vessel calibre occur in an attempt to autoregulate cerebral blood flow.

Patients and methods

We have been using near infrared spectroscopy (NIRS) to study changes in cerebral blood volume and cerebral oxygenation in preterm infants.[3] This technique enables the continuous monitoring of cerebral haemodynamics and is non-invasive. We report cycling of cerebral blood volume in a healthy preterm infant detected by NIRS. The observation was made fortuitously during a study to validate NIRS measurement of cerebral blood volume using jugular venous occlusion plethysmography.[4] Arterial blood pressure and transcutaneous blood gases were not monitored in this infant.

A girl of 31 weeks' gestation and 1735 g was studied at age 16 days. She had no major respiratory problems, and was healthy at the time of study with no ultrasound evidence of cerebral injury. The traces shown in the figure were collected while the infant was at rest in a quiet awake state. There was no significant variation in respiratory pattern or heart rate, and no procedures were performed during the period of study.



Cyclical fluctuations in cerebral blood volume (CBV) detected by NIRS and strain gauge.

Results

The upper trace shows the strain gauge signal indicative of occipitofrontal circumference and the lower trace shows the change in total haemoglobin as measured by NIRS. There are simultaneous rhythmic fluctuations in both traces at a frequency of 3·5 cycles/minute. This simultaneous change in total haemoglobin and occipitofrontal circumference would indicate cyclical changes in cerebral blood volume.

Discussion

The fluctuations in cerebral blood volume noted using NIRS and strain gauge plethysmography are of similar rate to that observed for CBFV using Doppler ultrasound. It seems likely that both phenomena have a common cause. The ultrasound determination of CBFV only relates to examination of one vessel, whereas NIRS and strain gauge plethysmography detect changes in cerebral blood volume over the whole cerebral vascular bed.[4] A change in cerebral blood flow is likely to affect both cerebral blood volume and CBFV.

The aetiology of these cyclical fluctuations is unclear. They have previously been reported in infants of up to 8 days of age, and have now been documented in a preterm infant of 16 days. Rhythmic variations in heart rate or arterial blood pressure have not been found in previous studies where cycling of CBFV was seen.[1] It is difficult to eliminate small cyclical changes in arterial concentrations of carbon dioxide using non-invasive techniques given the rapid response time that would be required. Anthony *et al* thought that a cyclical change in carbon dioxide tension causing cycling of CBFV unlikely as their infants were paralysed and ventilated.[1]

Cyclical changes in intracranial pressure have been noted in adults in association with coma, and have also been seen in severely asphyxiated infants, usually with poor outcome. This is very unlikely to be the cause of cycling CBFV as the majority of infants where this has been seen had no evidence of brain injury. Similarly seizures which can affect intracranial pressure and cerebral blood flow could theoretically cause such cycling, but no evidence of fits has been found in the babies studied. In our infant there was no history of asphyxia and clinically no evidence of convulsions.

The primitive phenomenon of an immature autoregulatory response suggested by Anthony *et al* remains the most likely mechanism.[1] Rhythmic changes in vessel tone occurring throughout both large and small arteries would result in the cycling in cerebral blood volume seen in our infant. It would be interesting, though technically very difficult, to use both Doppler and NIRS simultaneously to clarify this further. The clinical significance of this cycling pattern remains unclear.

Finally, it is clear that NIRS can detect changes in cerebral blood volume giving an indication of changes in cerebral blood flow. It is thus a useful monitoring technique that may serve to improve understanding of the pathophysiology of neonatal brain injury.

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Neonatal renal candidal bezoar

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Abstract

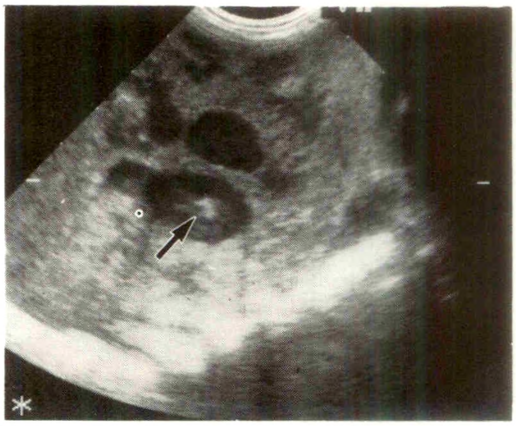
Renal candidal bezoar is uncommonly encountered in neonatal intensive care. An affected neonate who improved only after surgical removal of obstructive fungus from the renal pelvis and local irrigation with amphotericin B is described. The need for early consideration of surgical intervention is stressed.

Candida albicans is ubiquitous in the neonatal environment. Although superficial candidal infections of skin and mucosa are common, disseminated candidiasis and specific visceral candidal involvement occur infrequently and fungal obstruction of the urinary tract poses a specific management problem.[1] Predisposing factors include prematurity, intravascular catheters, broad spectrum antibiotics, immunosuppression, and total parenteral nutrition.[2]

Case report

A boy weighing 900 g was delivered at 27 weeks' gestation. The Apgar scores were 7 and 8 at 1 and 5 minutes respectively. He was electively ventilated from 20 minutes of age and transferred to us, aged 7·5 hours. Ventilatory support was required for idiopathic respiratory distress. By 40 days of age he had been weaned from the ventilator. He required phototherapy, parenteral nutrition, and repeated courses of antibiotics for proved bacterial infections. He developed posthaemorrhagic hydrocephalus that arrested spontaneously. By 2 months of age he was feeding, thriving, and was discharged.

At the age of 10 weeks he was readmitted for elective cryotherapy for stage 3+ retinopathy of prematurity. He appeared unwell, was moderately jaundiced, had abdominal distension, hepatosplenomegaly, and a palpable left kidney. An abdominal ultrasound scan showed bright echoes in the left renal pelvis compatible with a candidal bezoar (figure). *C albicans* was repeatedly cultured from blood and urine. The plasma urea concentration rose from 3 to 19 mmol/l and the serum creatinine from 40 to 145 μmol/l. Amphotericin B was started as an intravenous infusion over six hours at 100 μg/kg/day and gradually increased to 500 μg/kg/day over five days. Flucytosine in a dose of 100 mg/kg/day in four divided doses as an intravenous infusion over 30 minutes was also given. Two weeks later, despite systemic antifungal treatment, there was neither clinical nor biochemical improvement and both urine and blood cultures remained positive. *C albicans* was reported as sensitive to flucytosine and amphotericin B and serum concentrations were in excess of the minimum inhibitory concentration in vitro. An echocardiogram showed no evidence of valvular vegetations. A decision was made to use local antifungal treatment. A nephrostomy tube was placed percutaneously in



Ultrasound scan of left kidney in the long axis showing echobright lesion (bezoar) in renal pelvis.

the left renal pelvis under ultrasound guidance and secured by a skin suture. Local renal irrigation was carried out with 10 ml of sterile water containing amphotericin B at a concentration of 50 μg/ml instilled six times a day through the nephrostomy tube.

This tube became dislodged at 48 hours and at open nephrostomy a fungal pelvic ball was identified, removed, and a further nephrostomy tube was secured in the renal pelvis. Multiple abscesses were present throughout the renal cortex.

Within 24 hours there was appreciable clinical improvement and the plasma urea and creatinine concentrations returned to normal within four days. Systemic antifungal treatment and local amphotericin B irrigation were continued for six weeks, that is, two weeks after the last positive urine culture. The ultrasound scan showed complete resolution and normal renal echogenicity.

At the age of 10 months there was a mild left sided hydronephrosis on ultrasound but the dimercaptosuccinic acid (DMSA) scan showed good renal function. A mercapto-acetyl-triglycine renogram showed partial obstruction of the left ureter but the micturating cystourethrogram showed normal bladder and urethra without vesicoureteric reflux. Blood and urine cultures have remained sterile.

Discussion

Although superficial candidal infections are well recognised, systemic and renal candidiasis is less commonly described. Recently there has been an increase in reported cases. This may merely reflect an improved clinical awareness or alternatively may indicate a true increase as a consequence both of the increasing complexities of neonatal intensive care and the availability of non-invasive renal imaging techniques. In adults serum precipitin antibodies to candidal antigens have been valuable in the diagnosis of visceral infections.[3] In neonates the presence of intraleucocytic hyphae on buffy coat examination has proved useful in diagnosis of candidaemia (negative smear in our patient).[4] There are no accepted standard diagnostic criteria for neonatal urinary candidiasis in terms of colony count. It is preferable to examine and culture urine obtained by suprapubic aspiration rather than by a bag collection.

Ultrasound appearances depend upon the extent of involvement. The findings of bright echoes in a dilated renal pelvis of a child who has positive fungal cultures either in urine or blood is highly suggestive of a renal mycotic bezoar.

WHAT IS THE MECHANISM OF RENAL CANDIDAL INFECTION AND BEZOAR FORMATION?

In animals, large doses of *C albicans* injected intravenously have caused generalised candidiasis and multiple organ involvement, whereas smaller doses have produced transient candidaemia and only isolated renal involvement. These studies suggest that renal involvement starts as an acute pyelonephritis leading to multiple cortical abscesses and scarring within nine to 11 days after inoculation. At that stage candidal mycelia can be identified within the tubular lumen of the renal medulla and local proliferation leads to papillary necrosis, bezoar formation, and obstructive uropathy.[5] Alternatively it has been suggested that isolated renal involvement may represent an ascending infection. Additional predisposing factors include acidic and hypertonic urine, caliceal urinary stasis, and kidney anomalies.[6]

Therapeutic options for renal candidiasis include systemic antifungal drugs, local irrigation of renal pelvis via nephrostomy tube, and surgical removal of an obstructive candidal bezoar or nephrectomy. To our knowledge, there has been no report of a neonate with candidal septicaemia and renal candidal bezoar who has survived without surgical intervention.

Although parenteral antifungals are generally given for several weeks, as in our patient, we could find no therapeutic guidelines for renal pelvic irrigation in neonates. In adults, however, amphotericin B bladder irrigation has been used for six to 14 days in the treatment of non-invasive urinary candidiasis. In our patient we considered that local treatment should continue until blood, urine, and nephrostomy cultures were consistently negative and there was no longer ultrasound evidence of candidal bezoar. A six week course of irrigation was necessary and was well tolerated. Percutaneously placed nephrostomy tubes can become dislodged and their position should be checked after each instillation. A properly positioned nephrostomy tube will allow free backflow on aspiration and failure should be an indication to verify the tube position by ultrasound scan.

We feel that all neonates with systemic candidal infection must have an abdominal ultrasound scan to exclude renal candidal bezoar. Once recognised it should be managed by immediate percutaneous placement of a nephrostomy tube followed by local irrigation with amphotericin B in addition to systemic antifungal treatment. Treatment should be guided by clinical status and regular abdominal ultrasound scans. Open nephrostomy and surgical removal of the bezoar should be considered if: (i) clinical response is poor, (ii) renal function deteriorates, (iii) bezoar size fails to regress, and (iv) there are mechanical problems with amphotericin B irrigation.

Constant vigilance and early diagnosis of this insidious onset opportunistic infection managed as outlined above should improve the long term prognosis and preserve renal function.

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OBSTETRICS FOR PAEDIATRICIANS

Rhesus haemolytic disease

Martin J Whittle

Until the late 1960s when anti-D prophylaxis was introduced, stillbirths and neonatal deaths from rhesus isoimmune disease were significant contributors to the perinatal mortality rate, whereas most recent perinatal surveys report virtually no losses. Explanations for this include the crucial role of prophylaxis and the limitation of family size, the problem becoming worse with successive pregnancies.

In part, however, the reduction is artifactual, because some losses occur before 28 weeks and are therefore registered as abortions and not as perinatal deaths.

The reduction in the overall incidence of rhesus disease has meant that experience among obstetricians, paediatricians, general practitioners, and midwives is generally low necessitating the development of expertise concentrated in large regional centres from which management advice can be readily available. It should be remembered, however, that prevention is the most effective method of 'managing' rhesus disease, so it is vital to ensure that anti-D is administered at the correct time and in the correct dose after any potentially sensitising event.

Pathophysiology

Classically rhesus disease occurs because maternal anti-D antibodies cross the placenta and cause haemolysis of rhesus positive fetal red cells. Sensitisation occurs in rhesus negative women if rhesus positive fetal blood leaks into their circulation either spontaneously or by one of the events shown in the table. Most commonly leakage occurs when the placenta separates at delivery, and hence the rationale for anti-D administration (in a dose of at least 500 IU) within 72 hours of this event. Antibodies may develop during the first pregnancy probably as a result of spontaneous leakage, and the prophylactic use of anti-D during pregnancy (usually at 28 and 34 weeks) to neutralise fetal cells, has been attempted.

Events that may cause sensitisation in rhesus negative women if rhesus positive blood leaks into their circulation

Abortion:
  Threatened
  Spontaneous
  Induced

Ectopic pregnancy

Procedure related:
  Chorionic villus sampling
  Amniocentesis
  Fetal blood sampling
  Intrauterine surgery

Obstetric:
  Antepartum haemorrhage
  External cephalic version
  Delivery

Though anti-D is the most common antibody, others also produce disease including Rh C, D, E, c, and e, Kell, Kidd, and Duffy antibodies. All are IgG in configuration and capable of crossing the placental barrier. Regardless of type their haemolytic ability relates to their avidity, absolute concentrations being less important. This uncertainty about antibody activity means that great care must be taken when planning management. Relatively low concentrations of antibodies are sometimes capable of producing severe disease.

Steadily increasing fetal anaemia is almost certainly the result of haemolysis although there is a suggestion that anti-Kell, for example, may also suppress erythropoiesis. Extramedullary erythropoiesis starts in response to the anaemia, one effect of which is fetal hepatosplenomegaly. The liver becomes totally dedicated to the production of red cells and other activities are obtunded. Thus reduced albumin manufacture leads to hypoalbuminaemia, a fall in plasma oncotic pressure, and the development of hydrops. Further deterioration progresses to metabolic acidosis, high output cardiac failure, and death.

The timing of these events in pregnancy is to some extent unpredictable. The fetus is rarely affected before 16 weeks, probably because the antibodies do not cross the placenta until then. Thereafter timing depends on antibody type, quantity, and avidity together with the fetus's ability to respond. The point at which the changes become irreversible is also uncertain, though recent experience with a fetus whose first packed cell volume was only 0·04 suggests that cardiac damage may occur at about this point. The fetus survived several intrauterine transfusions and the hydrops resolved, but the baby died of unresponsive heart failure about eight days after delivery.

Assessment

About 15% of the population of the western world are rhesus negative, and if anti-D antibodies are not found at the time of booking, further checks should be made throughout pregnancy; the minimum recommendations are at 28 weeks, 34 weeks, and at the time of delivery. If antibodies are found at any time the mother should be recalled and the test repeated, preferably within two weeks. Non-rhesus antibodies will be screened for at the booking visit, and perhaps once more, later in pregnancy, and because they can act atypically their presence should be brought to the attention of the regional centre.

SEROLOGY

Titres of anti-D antibody below 4 IU/ml or, when the antibodies are only semiquantified, at or below 1 in 16 are very unlikely to produce serious fetal disease; in general this applies to other antibody systems too.

Once antibodies are present the frequency of measurement depends on their absolute titre and the past history. For example a titre below

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4 IU/ml requires measurements every two weeks but above this titre weekly assessments are sometimes desirable.

A titre above the critical 4 IU/ml (or 1 in 16) will indicate the need for further evaluation and once a value of 10 IU/ml has been reached advice from a referral centre should be sought. Below 5 IU/ml only 2% of babies have mild or moderate anaemia whereas at titres between 20 and 100 IU/ml, 10% may have severe anaemia (defined as a haemoglobin concentration of less than 70 g/l). When the antibody content exceeds 100 IU/ml, however, about 75% will have severe anaemia, and virtually all the remainder will have mild to moderate disease.

OBSTETRIC HISTORY

Traditionally the severity of rhesus disease has been judged from events in the obstetric history, the assumption being made that the disease becomes worse with each pregnancy. In general this is true but mild disease in the last pregnancy—for example, requiring only phototherapy at term—does not insure against the need for an intrauterine transfusion during the next pregnancy. The birth of a baby requiring exchange transfusion, one needing preterm delivery for suspected anaemia, and the miscarriage or stillbirth of a hydropic fetus, is particularly ominous. Information about earlier pregnancies should always be obtained and the father's blood genotype determined: it is important not to be coy about ensuring that the right partner is identified. The value of the history in planning management has remained controversial, but if the last baby was severely affected and the partner is homozygous for the D antigen it virtually guarantees that the next baby will be at least as badly affected and probably more so. An adage about the management of rhesus disease states that the easiest pregnancy to deal with was the last one.

AMNIOCENTESIS

The use of amniotic fluid to evaluate rhesus disease was described in the early 1960s and modified by several authorities, each of whom developed a unique protocol and different nomenclature; all of this has led to confusion. Liley, for example, who many regard as the father of fetal medicine, divised zones (upper, mid, lower) that represented risk categories based on the concentration of bilirubin in the amniotic fluid. Robertson retitled these so that the upper zone, in which the risk was highest, became zone 1 and the lower zone, zone 3, was the least affected. Freda in the United States, however, numbered the chart the other way round, designating the upper zone as zone 3. Another chart, described by Whitfield, superimposed the action line that demarcated Liley's middle and upper zones.

In spite of these difficulties the constitution of amniotic fluid has remained fundamental in the assessment of rhesus disease. In principle, the breakdown products from the haemolysed fetal red cells appear in the amniotic fluid as bilirubin, high concentrations indicating a serious condition. Bilirubin is quantified, usually by spectroscopic analysis, the maximum absorption for bilirubin being at a wavelength of 450 nm. The optical density difference is plotted on the Liley chart. Liley quickly realised that single measurements were of little use and that at least two measurements, preferably 10 to 14 days apart, were required.

Amniocentesis is indicated when anti-D exceeds 4 IU/ml, or a titre of 1 in 16 for other antibody systems. The timing of the first amniocentesis is vital and a rule of thumb is that it should be done 10 weeks before a rhesus related event occurred during the last pregnancy. For example, if the previous baby had to be delivered at 36 weeks' gestation because of a perceived rhesus problem then the amniocentesis in the next pregnancy should be at 26 weeks.

The current value of amniocentesis is debatable mainly because nowadays the more severe disease often becomes manifest between 20 and 24 weeks, when the Liley zones are invalid—they do not start until 27 weeks. Amniotic fluid analysis can give spurious reassurance in early pregnancy but the enormous experience that exists in its use in the evaluation of rhesus disease should not be disregarded and the technique still has a role in the management of the pregnancy at 27 weeks and beyond when the baby is not hydropic.

The use of amniotic fluid has several advantages. Firstly, it gives a better idea of the progress of the disease than does fetal blood sampling. Amniocentesis is a relatively easy procedure, which is probably less likely to stimulate the disease because it is nearly always possible to avoid the placenta. It can be done at most hospitals, although it is often wise to send the sample to the regional laboratory for analysis and interpretation.

ULTRASOUND

Modern ultrasound equipment allows the detection of early ascites so that with weekly or even twice weekly scans it is possible to delay any intervention, which will certainly be safer done later in the pregnancy; in addition fewer procedures will be required the later in pregnancy they are started. This non-invasive approach needs to be cautious, however, because the reliability of ultrasound in the detection of the early changes of ascites is uncertain and the required frequency of observations is unknown.

The biophysical profile can be used to monitor the fetal condition and evidence that the fetus is moving, breathing, and has good limb tone is welcome. In our experience, however, the profile does not seem to be sufficiently sensitive to detect subtle deteriorations in the fetal condition. The maternal perception of activity is often better, most mothers remarking that their baby moves less before a transfusion and more vigorously afterwards.

The value of Doppler waveform analysis from the fetal aorta and other vessels remains to be confirmed, and claims that a correlation exists between the readings and the fetal anaemia are interesting but not clinically useful.

FETAL BLOOD SAMPLING

The role of blood sampling in the evaluation of rhesus disease is still controversial, although there can be little doubt about its value in severe cases. The initial sample provides precise information about the fetal haematological state and blood type, the latter being important if the father is a heterozygote; if the baby is rhesus negative no further invasive procedures are required.

Although access to the fetal circulation is a major advance there are several important problems. Firstly, though the presence of anaemia indicates the need for transfusion, the course of action is less clear when the haematological state is normal. Arbitrarily the blood is resampled in one to two weeks but even this second sample may give little impression about what to do next. This is in contrast to the results from amniotic fluid, which will usually give a trend. It is theoretically possible for the fetus to maintain its haemoglobin concentration while showing evidence of haemolysis by a rising bilirubin concentration in amniotic fluid. Which test is most appropriate probably depends on the severity of the disease, fetal blood sampling being more valuable in the severest forms. The difficulty is in predicting the severity of each individual case.

Treatment

The decision to start treatment may be based on ultrasound evidence of ascites, a rising amniotic fluid bilirubin content, or haematological evidence of fetal anaemia, and (as discussed above) the method will depend on the severity of the disease.

The need to treat will depend to some extent on the gestational age and the presence of ascites. Clearly if amniotic fluid is showing a rising level crossing into the upper zone after 36 weeks then, in the absence of hydrops, delivery is undoubtedly the best policy. The development of ascites, even at this late stage is, I believe, an indication to carry out an intrauterine transfusion, because a fetus is more haemodynamically stable than a neonate and can more easily tolerate the transfusion. Once the fetus has been transfused it can be left in utero for a week to 10 days to stabilise and then be delivered. Certainly the delivery of a hydropic baby with severe anaemia and stiff lungs who requires immediate transfusion is a daunting paediatric problem, which is best avoided.

Intrauterine treatment is most commonly given by intraperitoneal and intravascular routes.

INTRAPERITONEAL TRANSFUSION

Liley was probably the first to realise that the intraperitoneal route could be used for blood transfusion and it became the paradigm for the treatment of severe rhesus disease.

A needle (usually 16 gauge) was inserted into the fetal peritoneal cavity under radiographic control. Once it was in place, a fine catheter was threaded down the needle into the cavity and the needle removed. The transfusion of concentrated cells was started at the rate of 1 ml/hour, the volume of blood given being calculated arbitrarily from gestational age (gestational age minus 20 multiplied by 10); thus at 32 weeks the required transfusion would be 120 ml. The survival rate from this procedure was good providing the fetus was neither hydropic nor too premature. The latter factor arose because of the technical problems associated with placing a needle under radiographic control into a mobile fetus of, say, 24 weeks' gestation. These problems have been largely overcome by using ultrasound guidance, which makes the intraperitoneal route more acceptable for fetuses at earlier gestational ages. Indeed there are advantages in combining intraperitoneal and intravascular transfusions. Unfortunately the intraperitoneal route is rarely, if ever, successful when the fetus has hydrops, probably because the lymphatics through which the blood is transported are waterlogged; this may also occur in simple ascites. The presence of ascites therefore makes intraperitoneal transfusion ineffective, and the intravascular approach has proved lifesaving in these seriously affected cases.

INTRAVASCULAR TRANSFUSION

The development of fetoscopy as a means of guiding the puncture of the funic vessels led to the first effective intravascular transfusions. Subsequently it became apparent that the same procedure could be done under ultrasound control, and since the mid 1980s this has been the method of choice.

Although the technical problems of intrauterine transfusion have been largely overcome a number of issues remain including the timing and frequency of transfusion, the volume of the transfusion and the rate at which it is given, the optimal route and the timing of delivery.

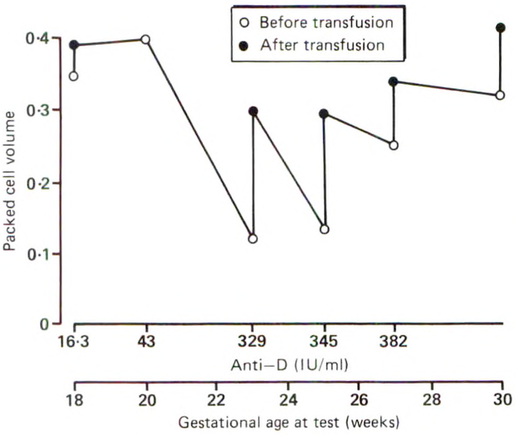
I have already discussed the timing of the first transfusion, and the calculation often involves a number of factors whose inter-relations are complex. Obviously the earlier the transfusion, the more hazardous the procedure even in the most experienced hands, and certainly the task is technically much more difficult before 24 weeks. The interval between each treatment is often judged arbitrarily, at least between the first and the second transfusions. We have found that the change in fetal haemoglobin concentration at this time can be difficult to predict and sometimes the packed cell volume falls suddenly (figure). Explanations include rapid sequestration of the transfused red cells by the fetal reticuloendothelial system, further haemolysis of the remaining fetal red cells, and leakage from the puncture site. Another possibility, which we are currently investigating, is that the fetoplacental vascular space is relatively contracted when the fetus is anaemic and its condition is poor. After transfusion fetal wellbeing improves and the vascular space expands, thereby diluting the red cells and lowering the haemoglobin concentration. This seems a likely explanation as the most rapid falls seem to occur among the sickest babies.

The volume of blood transfused must be sufficient to raise the packed cell volume to a reasonable level (usually about 0·4) without causing fluid overload, and normograms exist that provide a useful guide. The speed of transfusion is probably important, although the fetus seems to be able to cope with large volume transfusions sufficient at least to double the estimated fetoplacental volume. How such large transfusions are tolerated is unknown, but it may relate to the vast potential vascular space within the placenta which is capable of being further expanded by such vasodilating substances as atrial naturietic factor (and possibly prostacyclin) released in response to the fluid challenge.

The timing of further transfusions after the initial two is often easier to judge because the fall in packed cell volume against time becomes more consistent. The average drop of about 1–2%/day allows easy calculation of the timing of the next transfusion, but the traditional gap of two weeks (which was generated from the old intraperitoneal experience) seems often to be about right. The interval can, however, usually be increased to about three weeks after the third or fourth transfusion when the fetal condition has stabilised and only donor blood is circulating, and a combination of intravascular and intraperitoneal transfusions may extend this interval.

The route of transfusion needs to be chosen for each individual fetus, and probably to some extent depends on the stage of pregnancy. The cord root is used most frequently and is satisfactory so long as clear views are obtained. Though it is a relatively stable target it may be obscured by the fetus, which can usually be manoeuvred out of the way. As the pregnancy advances the fetus may not only overlie the cord root but also become less mobile making the intrahepatic portion of the umbilical vein sometimes preferable.

The timing of delivery has altered over the years, a balance being drawn between the chance of a vaginal delivery at a time when the fetal lungs are likely to be mature against the additional risks of repeated intrauterine transfusion. Probably delivery timed for about 34 to 36 weeks is best, and certainly the continuation of the pregnancy beyond this time may be unnecessarily hazardous.



Typical response of packed cell volume to transfusion in a severely affected fetus. The packed cell volume in cord blood was unusually low.

The outcome for these seriously ill fetuses when the intravascular route is used is surprisingly good, and about 80–90% of non-hydropic babies should survive compared with 70–80% of those with hydrops.

Neonatal care and paediatric follow up

The neonatal problems associated with severe rhesus disease virtually disappear when the fetus has received multiple transfusions, and because the baby's blood is virtually all donor in origin the haemoglobin concentration stays stable for a number of days. Exchange transfusion is rarely necessary, although a simple 'top up' may be required during the first few days of life. Of great importance is the fact that hyperbilirubinaemia does not usually occur, therefore reducing the need for an exchange transfusion. In contrast the hydropic baby even if born at full term may cause enormous paediatric problems that require intensive care, respiratory support, and—usually—multiple transfusions: mortality is often high.

Long term follow up of these severely affected babies is limited. Older published data would suggest that babies who have undergone intraperitoneal transfusion are no more likely than any other babies to develop mental or physical disabilities. The severely affected hydropic babies, however, usually died whereas nowadays, when intravascular techniques are used, they usually survive. Results of developmental testing of a group of previously severely affected babies from our own series showed no differences when compared with those of matched controls.

Conclusions

Rhesus isoimmune disease has become a rare condition. It is largely preventable by anti-D prophylaxis, although a small but appreciable group of cases remains. If untreated these babies have a high mortality or if they survive they provide major paediatric problems. Management in specialised centres where there are the facilities for carrying out intrauterine transfusions (often by the intravascular route) combined with high standards of neonatal care, has had a major impact on the outcome in these seriously ill babies.

Recommended reading

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CURRENT PRACTICE

Respiratory support using patient triggered ventilation in the neonatal period

A Greenough, A D Milner

Over the last 30 years, there have been dramatic improvements in the survival rates of neonates requiring intermittent positive pressure ventilation. This has resulted from the introduction of ventilators specifically designed for use in babies weighing as little as 500 g and also from numerous studies attempting to optimise ventilatory techniques.[1] Nevertheless, even in the most skilled hands, babies still die during the acute phase of respiratory failure; pneumothoraces have not been abolished, and chronic lung damage produced predominantly by barotrauma and lung tissue hyperoxia is an increasing problem to neonatologists.[2]

Respiratory activity during conventional intermittent positive pressure ventilation

It is well established that in the immediate neonatal period, the pattern of ventilation selected by the respiratory centre in the brain stem is heavily modified by mechanical reflexes from the lung and chest wall[3]; such reflexes may be provoked by positive pressure inflation.[4] The Hering–Breuer reflex will limit inspiratory activity while at other times, Head's paradoxical reflex may stimulate the baby to make inspiratory respiratory efforts in response to intermittent positive pressure inflation.[4] If these were the only reflex responses then intermittent positive pressure inflation would always be associated with either apnoea or synchronous ventilation. Unfortunately, if the ventilator rate is too slow and the inspiratory time too long, reflex activity will stimulate the baby to make expiratory efforts during periods of ventilatory inflation.[5 6] This greatly reduces the efficiency of ventilation and increases the risk of pneumothorax and barotrauma.[4] This problem can be reduced by paralysing all those 'fighting the ventilator',[7] but this is not without its complications. The baby is entirely dependent on adequate ventilator function, fluid retention is common, contractures may develop in the limbs,[8] and higher inflation pressures are often needed to compensate for the loss of the baby's albeit intermittent, contribution to ventilation.[7] An alternative, has been to tune the ventilator to the baby's own respiratory efforts, thereby inducing synchrony.[9] Unfortunately, this is not always possible,[5] and even when optimal settings are selected, asynchrony can still develop due to alterations in the disease severity, chemoreceptor drive, and in response to medical and nursing handling.

Theoretically, it should be possible to circumvent these problems if the baby's respiratory efforts are used to trigger the ventilator. This approach, patient triggered ventilation (PTV), has only recently become available for use in neonates.[10] In this technique, the peak inspiratory pressure, positive end expiratory pressure, and inspired oxygen, are set by the operator, but the rate is controlled by the baby's respiratory efforts. This has the potential advantage that the peak inspiratory pressure should be lower as the baby is contributing to transpulmonary pressure, and situations in which the baby is actively breathing out during a period of ventilator inflation should be eliminated. On theoretical grounds, this should reduce the incidence of pneumothorax and bronchopulmonary dysplasia.

Triggering devices

The performance of the triggering device is likely to be an important determinant of the success of PTV. The triggering device must have a high sensitivity and thus detect the maximum number of the infant's respiratory efforts. The trigger delay, the time from the onset of inspiration to the commencement of positive pressure inflation, should be as short as possible to ensure inflation occurs early in inspiration and does not continue into expiration. If the trigger delay is very long, the only method of preventing inflation extending into expiration and stimulating an adverse respiratory intervention[4] is to shorten inflation time to such an extent that the delivered volume is reduced. The trigger delay consists of two components, the time needed for the baby's respiratory efforts to reach the critical trigger level, which is dependent on the pattern of breathing adopted by the baby, and the response time or systems delay of the ventilator. Ideally, the systems delay time should not exceed 10% of the total inflation time; a systems delay of 36 ms permits a maximum ventilator rate of 83 breaths/min.[11]

Currently, changes in airway pressure, airway gas flow, and abdominal movement are used as trigger signals. Airway pressure is sensed by a pressure transducer connected by non-compliant tubing to a point on the patient manifold just proximal to the endotracheal tube. Airway gas flow can be detected using either a pneumotachograph or, more usually, paired thermistors mounted in the patient's manifold of the ventilator circuit. Abdominal movements are detected by a pneumatic capsule which, when taped onto the patient's abdominal wall, in the subxiphis-

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ternal position, senses changes in abdominal expansion which occur with respiratory efforts. Although successful in the short term, oesophageal pressure triggering devices have proved not to be suitable for long term use, as the continued presence of a balloon in the oesophagus stimulates peristalsis which interferes with the detection of the infant's respiratory efforts.[12]

Ventilator settings during PTV

The peak inspiratory pressure, the positive end expiratory pressure, and the fractional inspired oxygen are usually left unchanged when the baby is transferred from conventional ventilation to PTV and then subsequently modified depending on the response to PTV as determined by blood gas estimations. The inflation time does normally require to be shortened. Prolongation of the inflation time beyond 0·4 s reduces minute volume as the baby's spontaneous breathing rate is slowed, presumably via the Hering–Breuer reflex.[13] A long inflation time is also more likely to result in inflation extending into expiration, provoking active expiration.[6] A short inflation time below 0·2 s is not beneficial as this reduces the tidal exchange.[14] The optimal inflation time is determined by observation of the baby's respiratory efforts while receiving continuous positive airway pressure for up to 1 min.[15] Inflation time should be about equal to the spontaneous inspiratory time after deduction of the systems delay; this ranges between 0·04 and 0·1 s depending on the ventilator selected. The inflation time is then reduced if necessary until the baby's respiratory efforts are indistinct from the ventilator inflation.[15]

As preterm babies have a tendency to apnoea, particularly when unwell, it is essential to have a minimum ventilator back-up rate to ensure continuity of respiratory support. This is achieved by either dialling in a maximal permitted expiratory time or a minimum ventilator rate. Thus 'back-up' ventilator rate is usually selected in conventional mode immediately before conversion to patient triggered mode. If the baby fails to trigger the ventilator by the end of the selected expiratory time, a single positive pressure inflation will occur.

Synchronous intermittent mandatory ventilation

One problem associated with PTV is that the operator has no control over the ventilatory rate, other than by altering the inspiratory time. Thus, during weaning, only the peak inspiratory pressure, the positive end expiratory pressure, and inspired oxygen can be reduced. A recent improvement has been to build in a variable refractory period after the ventilator has fired, essentially inactivating the trigger for a number of the baby's own respiratory efforts. It is then possible to reduce the ventilator rates progressively by increasing this refractory period.[16]

Clinical trials on PTV

One study compared PTV delivered by the modified SLE 250 ventilator using the MR10 pneumatic capsule, and the airway pressure triggering systems.[17] The median trigger delay of the airway pressure sensor was 200 ms compared with 300–550 ms with the MR10. As a result, synchrony occurred more frequently using the airway pressure trigger, leading to a significantly greater tidal exchange. The airway pressure trigger also had a much greater sensitivity detecting up to 100% of the infant's respiratory efforts, compared with 70–90% from the MR10 respiration monitors.[17] The commercially available systems now available undoubtedly function better: preliminary studies indicate that, for example, the Draeger Baby Log and SLE HV 2000 have trigger delays of less than 100 ms in preterm babies with the respiratory distress syndrome.[18 19]

There have now been a number of studies attempting to define the optimal role of PTV. This is usually unsuccessful in infants of less than 28 weeks' gestation.[15] Such infants rapidly develop a metabolic acidosis; their respiratory efforts are irregular and often of insufficient magnitude to trigger the ventilator consistently. PTV also failed in nine of 13 infants greater than 27 weeks' gestation, but less than 24 hours of age.[20] In contrast, PTV has provided an alternative to conventional ventilation in babies greater than 28 weeks' gestation after the first 24 hours of age.[15] One study suggested that PTV may reduce the incidence of pneumothorax,[21] but unfortunately this used historical controls and there is no evidence from randomised trials to support this contention. PTV has also been attempted in those very immature infants who require ventilation beyond the second week of life due to chronic lung disease, but rarely provided a satisfactory alternative to conventional ventilation. In these babies, PTV was only successful in three out of 16 infants; the remaining 13 were either asynchronous or made only irregular respiratory efforts with deterioration in blood gases after only one hour.[22]

Prediction of failure of PTV

Gestational and postnatal age are important determinant factors of the PTV outcome.[15 22] Studying infants for only one hour on PTV provides useful information to assess if PTV will be successful in the long term.[15] Failure of PTV is likely to occur in infants whose oxygenation does not increase after one hour, compared with a similar period on conventional ventilation. A further indicator of failure is a triggering rate which is slow in relation to the infant's gestational age,[23] and an asynchronous respiratory interaction.

Summary

There are now a number of purpose built patient triggered ventilators for use in the newborn. These ventilators are triggered either by air flow or airway pressure changes, their triggering devices all have very high sensitivity and short systems delay. They all have the advantage that they perform well without inadvertent positive end expiratory pressure at the fast ventilator rates frequently triggered by immature infants. Despite all these improvements in both ventilator and trigger performance, PTV is still frequently unsuccessful in the most immature infants. We must conclude that the nature of the extremely preterm infant's respiratory efforts in the acute stage of respiratory illness may mean that PTV is unlikely to provide the optimal mode of respiratory support for this group of patients. Short term studies have suggested that those infants with relatively mild respiratory distress syndrome showed the greatest improvement in blood gases. These results suggest that PTV may have its most efficacious role during weaning and in the larger, more mature baby who is 'fighting the ventilator'.

Correction

In the article entitled 'Patient triggered ventilation using a flow triggered system' (M F Hird, A Greenough, *Arch Dis Child* 1991;**66**:1140–2) an incorrect model number of the SLE ventilator was given, the trigger delay of 200–250 ms applies to the SLE 250 and not the SLE HV 2000.

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PERINATAL LESSONS FROM THE PAST

Dr William Cadogan (1711–1797) of Bristol and the management of infants

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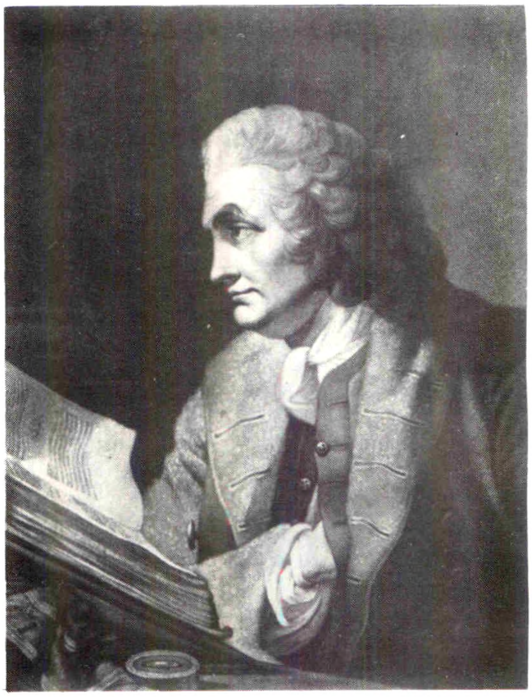
Apart from the fact that he was born in 1711, possibly in Cowbridge near Cardiff, not a great deal is known about William Cadogan's early life.[1] He studied medicine at Oriel College, Oxford between 1727–32 and then in Leyden when he obtained his MD in 1737. Nothing is known of his activities during the next decade until, in 1747, Farley's *Bristol Journal* describes him as 'an eminent professor of physic in this city'. He had married Frances Cochran, the daugher of a wealthy planter in Antigua, and in May 1747 their daughter was born, also named Frances. Cadogan's interest in the upbringing of young children was no doubt stirred by the advent of a baby in his own household and a year later he wrote *An Essay upon Nursing and the Management of Children from their Birth to Three Years of Age*[2] at the request of the Governors of the Foundling Hospital, an institution that had been opened in London by Captain Thomas Coram in 1741. This short pamphlet of just 34 pages earned Cadogan wealth, honour, and a lasting name in the history of paediatrics. During the next 37 years it ran through 12 editions and its honest commonsense did much to correct the appalling ignorance that existed at that time in respect to infant care.[3]



William Cadogan, 1711–1797.

'The art of physick has been much improved within this last century; by observing and following nature more closely, many useful discoveries have been made, which help us to account for things in a natural way, that before seemed mysterious and magical; and which have consequently made the practice of it more conformable to reason and good sense. This being the case, there is great room to fear, that those nurses who yet retain many of these traditional prejudices, are capitally mistaken in their management of children in general, and fancying that nature has left a great deal to their skill and contrivance, often do much harm where they intend to do good. . . . The truth of what I say, that the treatment of children in general is wrong, unreasonable, and unnatural . . . let any one, who would be fully convinced of this matter, look over the Bills of Mortality; there he may observe that almost half the number of those who fill up that black list, die under five years of age . . . Ought it not therefore to be the care of every nurse and every parent, not only to protect their nurselings from injury, but to be well assured that their own officious services be not the greatest the helpless creatures can suffer? . . . The mother who has only a few rags to cover her child loosely, and little more than her own breast to feed it, sees it healthy and strong, and very soon able to shift for itself; while the puny infant, the heir and hope of a rich family, lies languishing under a load of finery that overpowers his limbs, abhorring and rejecting the dainties he is crammed with, till he dies a victim to the mistaken care and tenderness of his fond mother . . . children in general are over-cloathed . . . The truth is, a newborn child cannot well be too cool and loose in its dress; . . . But, besides the mischief arising from the weight and heat of these swaddling-cloaths, they are put on so tight, and the child is so cramped by them, that its bowels have not room, nor the limbs any liberty, to act and exert themselves in the free easy manner they ought. This is a very hurtful circumstance; for limbs that are not used will never be strong, and such tender bodies cannot bear much pressure: the circulation restrained by the compression of any one part, must produce unnatural swellings in some other . . .

The feeding of children properly is of much greater importance to them than their cloathing . . . if we follow nature, instead of leading or driving it, we cannot err . . . Her design is broke in upon, and a difficulty raised that is wholly owing to mistaken management. The child, as soon as it is born, is taken from the mother, and not suffered to suck till the milk comes of itself; but is either fed with strange and improper things, or put to suck some other woman . . . were the child kept without food of any kind (for six or seven hours), till it was hungry, which it is impossible it should be just after the birth, and then applied to the mother's breasts; it would suck with strength enough, after a few repeated trials, to make the milk flow gradually, in due proportion to the child's unexercised faculty of swallowing, and the call of its stomach. Thus the child would not only provide for itself the best of nourishment, but, by opening a free passage for it, would take off the mother's load, as it increased, before it could oppress or hurt her; and therefore effectually prevent the fever; which is caused only by the painful distention of the lacteal vessels of the breasts, when the milk is injudiciously suffered to accumulate . . . When a child sucks its own mother, which, with a very few exceptions, would be best for every child and every mother, nature has provided it with such wholesome and suitable nourishment; . . . If I could prevail, no child should ever be crammed with any unnatural mixture, till the provision of nature was ready for it; nor afterwards fed with any ungenial alien diet whatever, at least for the first three months: for it is not well able to digest and assimilate other aliments sooner. I have seen very healthy fine children, that never eat or drank any thing whatever but the mother's milk for the first ten or twelve months. Nature seems to direct this, by giving them no teeth till about that time . . . Thus far nature, if she be not interrupted, will do the whole business perfectly well; and there seems to be nothing left for a nurse to do, but to keep the child clean and sweet, and to tumble and toss it about a good deal, play with it, and keep it in good humour.

The plain natural plan I have laid down is never followed, because most mothers, of any condition, either cannot, or will not undertake the troublesome task of suckling their own children; which is troublesome only for want of proper method; were it rightly managed, there would be much pleasure in it, to every woman that can prevail upon herself to give up a little of the beauty of her breast to feed her offspring; though this is a mistaken notion, for the breasts are not spoiled by giving suck, but by growing fat. There would be no fear of offending the husband's ears with the noise of the squalling brat. The child, was it nursed in this way, would be always quiet, in good humour, ever playing, laughing, or sleeping. In my opinion, a man of sense cannot have a prettier rattle (for rattles he must have of one kind or other) than such a young child. I am quite at a loss to account for the general practice of sending such infants out of doors, to be suckled or drynursed by another woman, who has not so much understanding, nor can have so much affection for it as the parents; and how it comes to pass, that people of good sense and easy circumstances will not give themselves the pains to watch over the health and welfare of their children; but are so careless as to give them up to the common methods, without considering how near it is to an equal chance, that they are destroyed by them'.

In 1749 Cadogan was elected a governor of the Foundling Hospital and in 1752 he resigned his post in Bristol and moved to London. He was 41. His success was immediate. Elected FRS in 1752, he was made physician to the Foundling Hospital in 1754, obtained MDs from both Oxford and Cambridge in 1755 and became a Fellow of the Royal College of Physicians in 1758. He was Censor to the College on four occasions and gave the Harveian oration twice, in 1764 and 1792. In 1761 he was appointed physician to the army and served with it in Portugal in the war with Spain for several months the next year until invalided home.

In 1771 Cadogan produced his second important work, *A Dissertation on the Gout* . . ., a disease which he blamed on indolence, intemperance and vexation, advocating for its treatment, activity, temperance and peace of mind. He did not spare his colleagues commenting on the 'precarious skill of prescribing doctors' and the 'ignorant but enterprizing and influential quacks'. The book brought a storm of abuse about his head to which he remained indifferent, confident in the soundness of his assertions. His wife Frances had died and in 1759 he remarried a Mrs Spencer and, when she died, a third wife, Miss Groen in 1772. But there were no further children. He died at the age of 86 in 1797 and was buried in Fulham churchyard.

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BOOK REVIEWS

Nutrition and Metabolism in Pregnancy. By Pedro Rosso. (Pp 324; £45 hardback.) Oxford University Press, 1990. ISBN 0–19–503928–9.

It is arguable that nutrition and metabolism in pregnancy cause more people to talk more nonsense more vehemently than any other aspect of obstetrics. As the author states, he 'firmly believes that well-designed nutrition programs could greatly benefit mothers and their unborn infants throughout the world' but 'I am also equally convinced that conclusive scientific evidence supporting my belief is lacking' and that 'the cause of maternal nutrition will be better served by those who prefer to be scientifically rigorous than militant'. Amen to that. Everyday practice is littered with dogma, either not supported or refuted by the evidence in the literature. Dr Rosso admirably reviews the many papers showing that pre-pregnancy maternal weight for height (the body mass or Quetelet index) is much more important than weight gain in pregnancy, and that for the bulk of the pregnant population who are of normal or above normal weight for height, weight gain is of little significance. And yet almost no-one in clinical practice routinely calculates the body mass index at booking (although it is the single most important predictor of low birth weight we know of). While in the UK each year, assuming that weighing and recording each pregnant woman's weight takes only two minutes at each of the average 12 antenatal clinic visits, a total of more than 36 years of client/staff time are wasted in fruitless communion with weighing scales! Add to this the many women who have labour induced unnecessarily for physiological weight loss at term, and the consequences of misinformation are staggering.

Dr Rosso reviews the huge literature in masterly fashion. He gives a precis of the most important papers, and his comments and analysis are objective and helpful. He covers the physiological changes of pregnancy, emphasising the central role of plasma volume expansion (and laying the myth that pregnant women commonly suffer from 'anaemia' rather than haemodilution). The section on maternal metabolism of vitamins and minerals documents that for most women in the developed world a normal diet is more than adequate for pregnancy needs, and the many claims for dramatic results from supplementation both in pregnancy and the neonatal period should be treated with deep suspicion. The section on fetal growth clearly indicates the difficulties of defining 'intrauterine growth retardation', with its many causes (infective, chromosomal, metabolic, as well as nutritional). The concept of 'normal weight growth retardation' (a good sized baby who has failed to reach its genetic growth potential) is well explained and explored. Recommendations emphasise the importance of a long term population strategy for nutrition, and the relative futility of short term intervention in pregnancy in women with a background of chronic dietary insufficiency over many generations.

This is an important book which will act as a valuable resource for workers in the area of nutrition, as well as providing a manageable introduction for those who wish to enter it. It is very readable, as well as being scholarly. The only improvement I can think of would have been a summary of conclusions, which could then have been photocopied onto brightly coloured paper and force read to all those conducting antenatal care!

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Diseases of the Newborn. Edited by H Taeusch, R Ballard, and M Avery. (Pp 1115; hardback.) W B Saunders Company, 1991. ISBN 0–7216–2476–6.

Most very sick babies are cared for without consulting books. Nevertheless every baby unit needs a large book for help with rare conditions and to check normal values, drug dosages, and the like. The other function of large texts is to provide junior staff with detailed information about common problems. There are at least two other major American neonatal texts but the biggest rival in the UK must be Roberton's large *Textbook of Neonatology*. How does this book compare?

The editors (from Boston, Chicago, and San Francisco) have recruited 66 contributors, of whom 65 work in the USA. There are 20 sections with a total of 116 chapters. The introductory section includes chapters on the history of neonatal care, ethical considerations, and the evaluation of treatment. Other large sections cover fetal growth and development, genetic diseases, infections and immunology, stabilisation and initial evaluation, and general principles of care. With the exception of the skeleton all major organ systems have their own section.

Chapters range in size from two pages on the foreskin and circumcision to 40 pages on cardiac malformations. In typical American style the authority of most chapters is enhanced by a lot of basic science at one end of the chapter and large numbers of references at the other. For instance there are 187 references cited in the chapter on maternal substance abuse. Lengthy lists provide another typically American feature. For example, a list of the causes of fetal hydrops takes up two thirds of the page. Although many of these lists are very useful, I will not be consulting the list on 42 causes of low birth weight.

I found something pertinent in this book about all the recent rarities that have challenged us locally. It is more encyclopaedic than Roberton's large textbook. It certainly has a larger pharmacopoeia (137 drugs listed compared with Roberton's 59), and even the dose of diphtheria antitoxin is stated.

It is disappointing that the book is generally stronger on basic science than on practical advice. The reader has to labour through 27 pages covering lung development and physiology to find barely three (not very good) pages on the practicalities of mechanical ventilation. This is unbalanced; the central technique of neonatal intensive care deserves more than three pages in a thousand page book. Similarly in the chapter on the management of bronchopulmonary dysplasia almost more space is given to an incomprehensible diagram about free radicals than to the management of the disease itself.

Roberton's large *Textbook of Neonatology* is a much better read than this book. On the other hand this book's account of the American way challenges parochial tendencies in non-Americans. And you get a lot of facts for your money.

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Annotation

Psoriasis in childhood

Psoriasis is a common probably polygenically determined papulosquamous skin disorder of unknown cause. An association has been found with the HLA antigen HLA-CW6. The risk for first degree relatives of an isolated case is at least 10% but children of two psoriatic parents have around a 50% risk of being affected.[1] It affects approximately 2% of the population of Europe and North America and is more common in white people. In childhood it is more common in girls. In a 1988 survey I found 31% of adult psoriatic patient remembered an onset before the age of 16 but in Scandinavia the figure is 45%.[2] Ten per cent of a large American sample had an onset before the age of 10 years.[3] Farber *et al* re-examined nine children with psoriasis in infancy 6–13 years later and found that seven still had recurrent psoriasis, although this was generally not severe.[4] One of these children had psoriasis from birth and congenital psoriasis has been reported previously.[5]

In children guttate psoriasis occurs more frequently than in adults and appears abruptly, often a week or so after a streptococcal tonsillitis or other infection and may be widespread. The small papular lesions have characteristic overlying silvery scales. The guttate eruption usually persists for three to four months resolving spontaneously but it can persist for over a year. After an attack of guttate psoriasis it is usual for psoriasis of some type to recur within the next three to five years.

The Köbner phenomenon in which lesions appear along the site of injury may be seen in active psoriasis. Parents should be warned that skin trauma—for example, scratches or sunburn—may result in psoriasis at such trauma sites.

Psoriasis vulgaris, the plaque type of psoriasis, is also common in children; as well as plaques, ringed and geographic patches of varying sizes may occur. Plaques may be encircled by a clear pale zone, the ring of Woronoff. Scalp psoriasis is typified by patchy thick scaling areas and when scales are removed some hair may be lost but almost always regrows. Pityriasis amiantacea describes a condition in which scalp patches occur showing white asbestos-like scales, which cling firmly to the hair shafts as they emerge from the scalp and extend some distance along them; in children it is often psoriatic.

Nail changes are seen particularly in chronic psoriasis and are uncommon in children, but onycholysis of finger nails (separation of the distal nail plate from the nail bed) and pitting may be seen and occasionally nail changes are seen with minimal skin involvement.

Pustular psoriasis is rare in children but abuse of the more potent topical corticosteroids in the treatment of ordinary psoriasis and sometimes their withdrawal may precipitate this form.[6] However, in children psoriasis may present as a pustular acrodermatitis involving one or two fingers and this may coexist with or be followed later by typical psoriasis elsewhere.

Psoriatic arthropathy is rare in children but may precede the onset of skin lesions. It may be initially misdiagnosed as juvenile rheumatoid arthritis but systemic manifestations associated with juvenile rheumatoid arthritis are usually absent.[7]

As regards treatment most children can be managed as outpatients. Bland preparations such as aqueous cream or coal tar solution 2% in emulsifying ointment are recommended for guttate psoriasis. Coal tar preparations are useful for psoriasis vulgaris and scalp psoriasis. Sunlight and ultraviolet light B have a beneficial effect in chronic psoriasis in most individuals but are contraindicated in acute guttate or other acute psoriasis.

A common time honoured regimen for plaque psoriasis is a tar bath followed by exposure to ultraviolet light B and then application of dithranol in Lassar's zinc paste with salicylic acid. Dithranol may irritate the skin and treatment should start with a low concentration. Patients/parents should be informed of the temporary brown skin staining dithranol produces. Short contact dithranol, preferably in the form of a cream (for example, Dithrocream, (Dermal)) applied for 20–60 minutes in the evening before a bath and bed is a modern effective treatment which allows freedom from clothes staining applications during the school day.

Sparing use of topical corticosteroids of mild or moderate potency does have a place in the treatment of face, ear, flexural, and genital lesions. Such preparations with their ability to suppress inflammation may sometimes also be used in combination with tar over limbs and trunk in irritant psoriasis.

An interesting recent treatment, so far limited to adult experience, is calcipotriol, a synthetic vitamin D analogue, applied in ointment form. Early evidence suggests this to be a safe effective preparation in moderate psoriasis,[8] and one of its actions is known to be suppression of epidermal keratinocyte proliferation, which is appreciably increased in psoriasis.

Although diet has no proved relationship to psoriasis oral fish oils may at times produce modest benefit.[9] Methotrexate[10] and oral synthetic retinoids[11] would be indicated only in rare uncontrolled erythrodermic psoriasis or generalised pustular psoriasis. Photochemotherapy (phototoxic psoralens used in combination with ultraviolet light A), long term use of which causes an increased risk of skin cancer, would also not be indicated in the routine management of childhood psoriasis. It is doubtful whether any place will be found in childhood psoriasis for cyclosporin, a potent immunosuppressant that is considerably nephrotoxic, but longer term adult studies will determine its safety.[12]

It is important to discuss with the parents of a psoriatic child all important aspects of the disease. Avoidance of emotional stress, where possible, may prevent a flare of eruption. Emphasis should be placed on spontaneous improvement and likely long remissions with treatment. The non-contagious nature of psoriasis should also be mentioned. Some families may wish to discuss the disorder with others and may wish to join the Psoriasis Association (7 Milton Street, Northampton NN2 7JG).

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ORIGINAL ARTICLES

Co-morbidity associated with fabricated illness (Munchausen syndrome by proxy)

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Abstract

Fifty six children who had been victims of fabricated illnesses and 82 of their 103 siblings were studied. In addition to the index fabrication, 64% of index children had had other illnesses fabricated by their mothers. Twenty nine per cent of the index children had a history of failure to thrive and 29% a history of non-accidental injury, inappropriate medication, or neglect. Seventy three per cent of the index children had been affected by at least one of these additional problems.

Eleven per cent of the siblings had died in early childhood, the cause of death not being identified. Thirty nine per cent of siblings themselves had had illnesses fabricated by their mothers, and 17% had been affected by either failure to thrive, non-accidental injury, inappropriate medication, or neglect.

First in 1977, and then subsequently, one of the authors (SRM) used the term Munchausen syndrome by proxy to describe cases in which a parent, invariably the mother, fabricated illness in her child or children and presented the problem to doctors.[1,2] Since that time, the number of reported cases has increased steadily, so that in 1987 a review considered 117 cases.[3] In that meta-analysis Rosenberg reported associated problems for the index child, including physical abuse in 1% and failure to thrive in 14%. Unusual deaths of siblings, and probable fabricated illnesses in other siblings, were mentioned but could not be assessed accurately because of the limitations of meta-analysis.[4] Our experience is that this 'co-morbidity' of index children and siblings may be considerably more prevalent. We believe that the best way to assess this is by the systematic study of the original case records of a series of affected children and their siblings.

Patients and methods

We reviewed a large number of cases of Munchausen syndrome by proxy which had been identified over a 13 year period from 1976 to 1988. This was possible because one of the authors (SRM) had been consulted, by professional colleagues, about cases from many parts of the UK. The cases met the following four criteria modified from Rosenberg and Meadow[2,3]:

(1) Illness in a child is fabricated by a parent, or someone who is *in loco parentis*.
(2) The child is presented for medical assessment and care, usually persistently, often resulting in multiple medical procedures.
(3) The perpetrator denies the aetiology of the child's illness.
(4) Acute symptoms and signs of illness cease when the child is separated from the perpetrator (almost always the mother).

Hospital case notes of index children were examined for evidence of failure to thrive, non-accidental injury, inappropriate medication, neglect and fabricated illness, before or at the same time as the identification of the index fabrications. Failure to thrive was recorded when this term was identified in the notes, or when there was evidence that the child had significant problems gaining weight which improved on hospital admission or other change of environment. Non-accidental injury was recorded when this had been decided by a case conference or appeared to be the most probable explanation of injuries in the light of an extended history of each child. Where possible the case notes of all siblings in each family were examined similarly. The circumstances of any deaths were examined. In many cases the general practitioner's notes were also examined. The case notes were examined also for continuing problems after the time of the index fabrication. The latter information was collected for a follow up study which will be published separately.

Initially 62 families were selected from about 100 families in which a child had suffered from the effects of a fabricated illness. They were selected on the basis of their recent address being known and availability for the study (including the fact that we believed we had, or could obtain, comprehensive medical records relating to the index child and siblings). During the course of the investigation it became apparent that we had insufficient information on six families, and therefore this part of the study was limited to 56 families.

Results

TYPES OF FABRICATION

The 56 families were grouped according to the most serious variety of fabrication for the index child in each family. The resulting four groups (smothering, poisoning, seizures, and miscellaneous) are shown in table 1.

For the smothered group (15 children; eight boys) the usual story given by the mother was that the child had stopped breathing and went blue (cyanotic/apnoea attacks) or had a fit. The period over which the suffocations occurred ranged from 1–47 months (median 9 months). The number of episodes of suffocation for each child ranged from 2–400. The median age at discovery was 15 months.

Table 1 Co-morbidity for 56 index children: the problems before recognition of the index fabrication

Variety of Munchausen syndrome by proxy	*No of index children*	*Problem*			*Total No affected by problem*
		Failure to thrive	*Non-accidental injury, neglected, or medicated*	*Other fabrications*	
Smothering	15	5	2 (2)	5	8
Poisoning	15	6	3 (1)	12	14
Seizures	14	1	4 (1)	10	10
Miscellaneous	12	4	7 (3)	9	9
Totals	56	16	16 (7)	36	41
% Of index children		29	29	64	73

Figures in parentheses refer to children also affected by failure to thrive (previous column). 'Other fabrications' refers to symptoms or illnesses in addition to the index fabrication.

The poisonings (15 children; eight boys) were carried out with a variety of substances: common salt, salt+hypnotic, lactulose, phenobarbitone, phenytoin, promethazine, 'Campden tablets' (sodium metabisulphite), amitriptyline, imipramine, lorazepam+imipramine+Milk of Magnesia, diazepam+De-Nol+aspirin. The children were usually presented to doctors with drowsiness or were said to have had a fit. In one case laxative administration either maintained or caused diarrhoea. The age of the children at the recognition of the poisoning ranged from 7 months–8 years. Two index children died from the poisonings. Additionally 11 other children (including siblings), classified here in other groups, had received medication. In some cases this had been oversedation by the mother, in other cases young children had taken medicines, not prescribed for them, in large doses. For a number of these 'overdoses', hospital admission notes recorded the ingestions as 'accidental'. In hindsight some of these ingestions were probably not accidental.

The 14 children (seven boys) in the third group had stories of seizures fabricated by their mothers, in some cases over many years, leading to extensive inappropriate medication for epilepsy. However, at the time of the discovery, there was no evidence that the mothers had caused direct physical harm to their child.

The 12 children (four boys) in the 'miscellaneous group' had a variety of fabrications imposed on them. These included haematemesis, haematuria, haemoptysis, urinary tract infection, glycosuria, pyrexia (by altering a temperature chart), vomiting, food allergy, and cancer. In two cases skin rashes were directly caused by abrasion.

CO-MORBIDITY FOR INDEX CHILDREN

Concerns recorded by professionals about failure to thrive, non-accidental injury, inappropriate medication, neglect, and additional fabrications, before or at the same time as the recognition of the index fabricated illness, are shown for each of the four groups in table 1. It can be seen that failure to thrive had been present in almost one third of cases (and in a half of these cases there had additionally been either a non-accidental injury or neglect). In total eight children had actually suffered from a non-accidental injury (with one of these also suffering neglect and one also receiving inappropriate medication), while six other children had suffered from neglect and a further three had been inappropriately medicated (not detailed in table). A large proportion (64%) had had more than one problem or illness fabricated. In the poisoned group this was as high as 80%. Overall, for 41 of the 56 index children (73%) there had been either failure to thrive, non-accidental injury, inappropriate medication, neglect, or they had been subject to more than one fabrication.

PROBLEMS FOR SIBLINGS

Forty three of the 56 index children (77%) had one or more siblings at the time of our investigation (table 2). Detailed records were available for 82 of these 103 siblings; incomplete information was available for another 21 siblings because of lost contact as a result of the child reaching adulthood and moving, or files being missing. We concluded that a large proportion of the siblings (39%) had themselves been the subject of fabricated illnesses, and 17% had suffered from either failure to thrive, non-accidental injury, inappropriate medication, or neglect. Seven siblings had received medication inappropriately.

Thirteen siblings had died and for 11 of these the reason was not medically conclusive at the time. The two deaths with identified causes were due to prematurity and congenital heart disease and occurred at 7 days and 2 months, respectively. One of the other deaths was in the first week of life; the remaining 10 occurred between the ages of 3 months and 18 months (median 10 months). Overall, 43% of siblings were affected by one or more of these problems; they came from 29 of the 43 families with more than one child.

Discussion

Some of the cases reported here have been reported in the literature, most commonly as single case reports, and some were probably included in Rosenberg's comprehensive litera-

Table 2 Morbidity and mortality for 103 siblings from 43 families

Variety of Munchausen syndrome by proxy	*Incomplete data*	*Total No of siblings*	*No of siblings*			*Total No affected*
			Victims of Munchausen syndrome by proxy	*Failure to thrive, non-accidental injury, neglected, or medicated*	*Died of uncertain cause*	
Smothering	0	25 (12)	12 (8)	4 (3)	8 (6)	14 (9)
Poisoning	0	26 (12)	8 (6)	5 (4)	3 (3)	10 (8)
Seizures	10	30 (11)	15 (8)	4 (2)	0	15 (8)
Miscellaneous	11	22 (8)	5 (4)	5 (4)	0	5 (4)
Totals	21	103 (43)	40 (26)	18 (13)	11 (9)	44 (29)
% Of total siblings			39	17	11	43

Figures in parentheses refer to number of families.

ture review of 117 cases.[3] We believe this to be the first systematic study, using original case records, to look at the co-morbidity of victims of fabricated illness and their siblings in a consecutive series of families referred to one centre. Failure to thrive (29%) and non-accidental injury (18%) were significant associated problems, as were inappropriate medication and neglect. The increased mortality of siblings has been noted before[5-8] and is confirmed by our study for siblings of smothered and poisoned index children. Most siblings do not die but it is alarming that 39% were victims of fabricated illnesses themselves and a substantial proportion were also affected by failure to thrive, non-accidental injury, inappropriate medication, and neglect.

The high morbidity rates may reflect the severity of abuse represented by the index cases. Most fabricated illness involves the mother merely inventing an illness story for the child, without resorting to direct physical action herself. It is relevant that more than half of the index children in this study had suffered from the direct actions of their mothers (by suffocation, poisoning, or skin abrasion) as well as invented false illness stories. It is likely that the under-reporting of co-morbidity in previous reports results partly from the problems not being sought systematically, particularly in siblings, and also from the difficulties in obtaining original case records, including the general practitioners' files. In relation to failure to thrive it should be recognised that in some cases the nature of the fabrication caused the chronic ill health, while in others it seemed to be a separate problem, predating the fabrication.

In this study we have identified specific problems before or at the same time as the identified fabricated illness. We have not specifically addressed the issue of emotional abuse which is difficult to identify and describe, especially retrospectively.[9] Other authors have described the psychological morbidity of the victims of the Munchausen syndrome by proxy in a number of children.[10] Continuing problems, including new fabrications or other new abuse, as well as emotional or behavioural disturbance in these children are the subject of a separate study.

The high morbidity rates for the siblings almost certainly are an underestimate, particularly as we were unable to obtain full data concerning one fifth of the siblings. Moreover, a number of the siblings, mostly those later in birth order, had been protected by legal orders or were not living with their mothers at the time of our study and so were at reduced risk of abuse. For all these reasons the figures for associated morbidity in the index children and for morbidity in the siblings should be considered as a minimum.

The implications for the management not only of the index children in cases of fabricated illness, but also of the siblings, are clear. In a family where this behaviour has occurred, the risk to all children in the family, of a variety of abuses and neglect, is high. Therefore the relevant professionals, usually the paediatrician, a social worker, and a child psychiatrist, should carry out a detailed assessment, in conjunction with the general practitioner and health visitor, of all the children and the parenting behaviours of mother and father.[11-13] In order to ensure the safety, and normal physical and emotional development of the children, if they remain in the family, professional involvement will usually be necessary until they are adult and usually will need to be on a statutory basis.

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Comparison of BCG vaccination at birth and at third month of life

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Abstract

Tuberculosis is an important health problem in developing countries and the BCG vaccine plays an important part in preventing the disease. There are different reports about the preventive value of BCG. Some of them claim that it is satisfactory while others suggest that it provides little protection. There are also varying ideas about the optimum time to vaccinate babies, some studies suggesting that late vaccination confers a high degree of protection. This prospective controlled study has been undertaken to evaluate the value of BCG vaccine given to babies during their first three days of life versus its value when given in their third month of life. Evaluation was measured by the results of tests with purified protein derivative (PPD), by vaccine scars, and by the complications of the vaccine. It was found that BCG given at the end of the third month provides a higher rate of response and fewer complications than when given during the first three days of life.

BCG plays a significant part in protection against tuberculosis, which is one of the most important problems in developing countries. Nevertheless, the protective effect of vaccine remains a highly controversial subject, and has been reported to range from 80% to less than 5%.[1–6] In many countries the first BCG vaccine is received at birth, but it has been suggested that this requires further evaluation.[1 7 8] A controlled prospective study has been recommended[1 7] to compare BCG results from vaccination at birth and those at the third month of life. This prospective controlled study was planned to compare tuberculin response, BCG scar, and the complications of the vaccine given in the first three days compared with the third month of life.

Subjects and methods

The subjects selected for the study were healthy, full term babies of over 2500 g born either in the Uludağ University Medical School Hospital or City Maternity Hospital in Bursa between October 1989 and January 1990. All the babies were followed up to 12 months. Babies who had a history of tuberculosis among their family or close contacts were excluded from the study.

Babies were randomly divided into two groups. Four hundred babies in the first group (group I) were vaccinated with BCG intradermally in the left shoulder in the first three days of life, and the second group of 400 babies (group II) was vaccinated in the same manner at the end of the third month (90±3 days) of life. Vaccines were given to both groups by the same trained personnel. At the beginning of the study the mothers of the babies under study were carefully examined and their BCG scars and induration of purified protein derivative (PPD) were recorded. For the babies in group II, a PPD test was carried out before the BCG vaccination. The babies in both groups were examined every three months until they were 12 months old, PPD tests were performed three months after BCG vaccination and at the end of the first year. A full examination was performed in the follow up and BCG complications were recorded. Lymphadenopathies of more than 10 mm maximum diameter and showing abscess formation and fistulisation were accepted as complications of BCG vaccine. Seventeen babies from the first group and 21 babies from the second group were excluded from the study as they had other diseases.

The same lot number of BCG, from Canada Connaught Laboratory, was used in both groups, and given in 0·05 ml (0·05 mg) doses. PPD from Denmark Statens Seruminstitut (RT-23 Mantoux test) was given intradermally to the volar surface of the forearm in 5 tuberculin units/0·1 ml doses. Seventy two hours later the induration caused by PPD was measured horizontally and vertically and the average of the measurements was recorded. During the controlling examinations BCG scar and complications were also measured and recorded.

Statistical comparisons were by Student's t test and z (normal distribution) test between groups.

Results

The number of babies who came to all the follow up examinations in group I was 313 (78%) and in group II was 334 (84%). Mean (SD) birth weights were 3370 (41) g in group I and 3410 (36) g in group II; statistical analysis revealed no significant difference. Weight gain was similar in the two groups. The feeding conditions were also similar. There were 169 babies (54%) in group I and 172 (52%) in group II who had breast feeding only; while 120 babies (38%) in group I and 128 (38%) in group II were fed by both formula feed and breast milk. The remaining 24 babies (8%) in group I and 34 (10%) in group II were fed by formula only. There were no significant differences between the groups.

As is seen in table 1, when PPD results were compared the diameter of the area of induration

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Table 1 Diameter of area of induration (mm) after the PPD test, comparing BCG given in the first three days (group I) and at the end of the third month (group II). Results are mean (SD)

	Group I (n=313)	*Group II (n=334)*	*p Value*
Three months after BCG	6·9 (3·8)	10·4 (4·3)	<0·001
12 Months old	8·4 (4·8)	10·8 (4·5)	<0·001

Table 2 The distribution of cases having PPD results of less than 5 mm induration. Results are number (%)

	Group I	*Group II*	*p Value*
Three months after BCG	122 (39)	43 (13)	<0·001
12 Months old	104 (33)	43 (13)	<0·001

Table 3 Details of the BCG scar at the end of the 12 months

	Group I (n=313)	*Group II (n=334)*	*p Value*
No (%) of cases not having scar	22 (7)	2 (0·6)	<0·001
Mean (SD) average scar diameter (mm)	3·6 (1·4)	4·4 (1·1)	<0·001

Table 4 Comparison of the BCG complications. Results are number (%)

	Group I	*Group II*	*p Value*
Lymphadenopathies (more than 10 mm)	52 (16·6)	17 (5·1)	<0·001
Lymphadenopathies with fistulisation	9 (2·9)	8 (2·4)	NS

is significantly larger after vaccination in the third month compared with those vaccinated in the newborn period; this was true for the comparison made three months after vaccination and also at the age of 12 months.

The distribution of those PPD results that were less than 5 mm in diameter are shown in table 2. The diameter of area of induration was significantly smaller in the babies that were vaccinated in the first three days of life compared with those vaccinated at three months.

The comparison of the BCG scars (table 3) shows that there were fewer and smaller scars in group I compared with group II.

As is seen in table 4, the number of lymphadenopathies with a diameter of more than 10 mm was found to be less in group II than in group I.

Discussion

For the prevention of tuberculosis, early detection and treatment of the cases and finding their contacts are essential. To eliminate the disease it is necessary to improve living conditions and use chemoprophylaxis or BCG vaccination. Eighty per cent of the world's population is living in the developing countries and it is very hard to improve their living conditions. For this reason BCG vaccination is accepted as one of the most important protective measures against tuberculosis. It is compulsory in 64 countries and is officially recommended in the remaining 118 countries and territories.[1,7] Although BCG has been used for more than 60 years, its protective value is still under discussion. Studies have shown that the efficacy of the vaccine varies between 5 and 80%.[1,6] Rosenthal *et al* state 'The usefulness of vaccination has been questioned on the basis that since the majority of cases of tuberculosis occur among the tuberculin positive individuals, and that, therefore BCG vaccination of the tuberculin negative portion of the population would not exert much influence on the incidence of disease. This misses the point that, had the tuberculin positive individuals been vaccinated prior to the time of their initial exposure to virulent tubercle bacilli, the incidence of tuberculous disease in this group might have been reduced to an appreciable degree. This situation actually provides a strong argument for the vaccination of infants and children, in areas of high incidence, against tuberculosis, with revaccination at suitable intervals in order to maintain as high a level of immunity as possible.'[9] It can be postulated that in developing countries BCG still plays an important part in the control of tuberculosis. Today BCG is used in the neonatal period in many countries. But there is little information on the efficacy of BCG vaccination in the newborn. In a previous study conducted in England, 149 Asian children who received BCG vaccine shortly after birth were reviewed at the age of 22 months and half of them had a negative response to tuberculin.[7]

The immunity provided by BCG is controlled with the PPD-S test 6–8 weeks after vaccination. Since implementation and validation of the PPD test is a simple procedure, it provides an easy assessment of acquired and/or natural immunity of individuals or populations. Our study has shown that when BCG is given at the end of the third month a better PPD response is obtained than when it is given in the first three days of life. The proportion of cases that did not produce a BCG scar is much less in those vaccinated at the end of the third month.

Certain complications of vaccination such as suppurative adenitis and BCG osteomyelitis are more common in newborn infants.[10] In some recent immunisation programmes BCG has been given a few months after birth. Studies are being carried out to establish whether vaccination induces a better immune response with less risk of complications at this age rather than during the newborn period.[7]

In this study the proportion of the lymphadenopathies larger than 10 mm diameter was found to be more in the babies who were vaccinated in the first three days than in those who were vaccinated at the end of the third mohth of life. The proportion of lymphadenopathies showing abscess formation and fistulisation was found to be similar in both groups.

We gave no treatment for complications except in the case of lymphadenopathies where abscesses were aspirated and fistulae dressed.

Our results show that BCG given at the end of the third month is more effective and gives a higher rate of PPD response and fewer complications of lymphadenopathy than BCG given in the first three days of life. According to these findings, it is recommended that practice be change in those countries in which BCG is given to newborn infants, and that the vaccine be given at the end of the third month instead. As our study shows that BCG vaccination at the third month gives more strongly positive

Mantoux tests at the end of the first year, our expectation is that protection from tuberculosis will be more powerful. This assumption is based on the fact that these babies will have a stronger cellular immunity. The prevention of tuberculosis should be the next subject for evaluation. We hope that the further studies will help to find the optimum time for BCG vaccination to provide the best immunity.

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Conditions accounting for substantial time spent in hospital in children aged 1–14 years

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Abstract

To identify the clinical conditions associated with substantial time spent in hospital by children aged 1–14 years, records of children admitted to hospital in 1975, 1979, and 1984 were studied. Analysis was by linkage of abstracts of routine records of hospital inpatient care in six districts in southern England covered by the Oxford record linkage study. The total time spend in hospital in the acute specialties each year was calculated by summing the lengths of stay of all episodes of care for each child in each year. First, admissions with long median times in hospital per child admitted were identified. These included, notably, fracture of femur and, in the later years, leukaemia, other malignant neoplasms, and congenital disorders of metabolism. Second, conditions were identified which accounted for large numbers of children with lengths of stay of five days or more. These included, in particular, congenital anomalies, asthma, and appendicitis. Third, conditions were identified which accounted for the largest numbers of bed days used. These included congenital anomalies, hypertrophy of tonsils and adenoids, asthma, otitis media, appendicitis, and head injury. Median time spent in hospital per child admitted declined for most conditions but increased for leukaemia, other malignant neoplasms, and congenital disorders of metabolism. Admission rates for children who spent five days or more in hospital each year declined for all common conditions except asthma which increased. Total numbers of beds used increased for asthma and otitis media but declined for all other common conditions.

The adverse emotional effects that may follow long periods of hospitalisation of children are well documented.[1–3] A great deal has been accomplished in minimising these effects by the introduction of unrestricted visiting by parents to children, the use of day case care, other short stay management, and the use of special teachers and play leaders. Nevertheless, long periods of hospitalisation are unavoidably upsetting for children.

The National Association for the Welfare of Children in Hospital has recommended that children should be admitted to hospital only if treatment at home is not possible, and that lengths of stay should be kept to a minimum.[4] The duration of episodes of hospital inpatient care for children has declined steadily for many years and, despite a considerable increase in rates of admission and readmission,[5] the total amount of time spend in hospital by children has fallen.[6] The aim of the study reported here was to determine (i) which conditions were associated with the lengthiest periods of hospitalisation in children aged 1–14 years and (ii) to investigate the extent of changes over time in the use of hospital care for the treatment of each of these conditions in this age group. We used medical record linkage to calculate the total time spent in hospital each year by each child with each condition.

Methods

The Oxford record linkage study includes brief abstracts of hospital records, birth registrations, and death certificates collected such that it is possible to link together episodes relating to the same individual. The present study included all general hospital admissions between 1975 and 1985 of children aged 1–14 years at admission who were resident and treated in the six districts of the Oxford region covered by record linkage (total population 1·9 million people). The lengths of stay of all episodes of care for each child, excluding those for mental illness and mental handicap, were summed to give a total time in hospital per child per year. Children admitted in 1984 were followed up into 1985 for the full 365 days after their last birthday.

For children who had more than one episode of care in the year, the principal diagnosis of the longest episode was taken as the underlying condition. For example, if a child had diabetes mellitus recorded as the principal diagnosis in the longest episode and other shorter admissions for respiratory infections, the total days in hospital were regarded as those spent by a child with diabetes mellitus. This was done as a means of simplifying the aggregation of episodes in a year under a single disease heading for each child.

Diagnoses were analysed using the three digit categories of the International Classification of Diseases (ICD8 and ICD9).[7 8] Where indicated, closely similar diagnoses were grouped (for example, the three ICD codes for appendicitis). Data are presented on time spent in hospital by children admitted in the calendar years 1975, 1979, and 1984. The terminology in the tables is from ICD8.[7]

Conditions in chapter XVI, which covers symptoms and ill defined conditions, were excluded as main diagnoses from the analysis because of their imprecision and because of difficulty matching ICD8 and ICD9. They are included when they occurred as admissions for

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children with a substantive main diagnosis and counted as the latter.

Results

Conditions which resulted in substantial time in hospital were defined in three ways. Firstly, conditions were identified that resulted in a median time in hospital per child admitted of five days or more: table 1 shows all conditions for which at least 30 children had a median stay of five days or more in at least one of the three years. The longest median stays were recorded for fractured femur, osteomyelitis, osteochondrosis, leukaemia and other malignant neoplasms, the code for congenital disorders of metabolism (which includes cystic fibrosis), certain congenital anomalies, cerebral spastic infantile paralysis (which covers cerebral palsy), and renal failure. In general, median times spent in hospital declined over the years. Median times increased for leukaemia, other malignant neoplasms, and congenital metabolic disorders.

Secondly, conditions were identified where at least 50 children in any one year had spent five days or more in hospital (table 2). This categorisation would, of course, identify conditions with long median stays, as in table 1, providing they were not rare. In addition, it identifies common conditions where, though the median time in hospital may be short, none the less there are substantial numbers of children with long stays. Thus, for example, although the median length of stay for asthma was three days, there were 495 children in the three years shown in table 2 who spent five days or more in hospital per year. In table 2 the number of children who spent five days or more in hospital is also expressed as population based rates per 10 000 children aged 1–14 years and as percentages of children admitted with each condition. The conditions which accounted for the largest groups of children who spent five days or more in hospital included appendicitis and congenital anomalies in which admission rates for such 'long stay' patients declined strikingly and asthma which showed a striking increase in such patients. Other conditions for which rates declined included diabetes mellitus, upper

Table 1 Conditions with median total times in hospital per child admitted of five days or more in at least one year: number of children with each condition and median total days in hospital per child

Diagnosis	*ICD8 code*	*ICD9 code*	*No of children*			*Medicn time in hospital/year*		
			1975	*1979*	*1984*	*1975*	*1979*	*1984*
Diarrhoeal disease	9		243	26	50	4	5	2
Leukaemia	204–7		29	35	12	7	4	16
Malignant neoplasms	140–203, 208–9		50	36	29	9	8	11
Diabetes mellitus	250		158	131	112	9	7	5
Other congenital diseases of metabolism*	273	277	19	22	30	6	12	11
Purpura	287		55	40	46	7	5	3
Cerebral spastic infantile paralysis	343		40	30	47	11	8	7
Pneumococcal pneumonia	481		54	64	72	5	4	3
Appendicitis	540–2		856	685	509	6	5	4
Renal failure	580–3	580–6	25	31	27	8	10	8
Eczema and dermatitis	692		24	33	14	9	9	6
Osteomyelitis	720	730	36	27	19	19	16	8
Osteochondrosis	722	732	61	63	39	19	15	9
Spina bifida	741		34	26	14	8	8	3
Congenital anomalies:								
Of heart	746		32	6	15	11	4	3
Cleft palate	749		35	23	30	8	5	4
Of musculoskeletal system	754–6		220	190	163	9	6	5
Fracture of femur	820–1		95	81	80	28	32	28
Burns	940–9		91	92	78	8	7	3
Total childhood population (aged 1–14 years)			458 500	429 500	396 400			

*Includes cystic fibrosis.

Table 2 Conditions for which 50 children or more spent five days or more in hospital in at least one year: number of children who spent five days or more in hospital, such children expressed as a rate per 10 000 children in the population aged 1–14 years, and as a percentage of all children admitted to hospital with each condition

Diagnosis	*ICD8 code*	*ICD9 code*	*No of children*			*Rate/10 000*			*%*		
			1975	*1979*	*1984*	*1975*	*1979*	*1984*	*1975*	*1979*	*1984*
Diarrhoeal disease	9		89	13	6	1·9	0·3	0·1	36·6	50·0	12·0
Diabetes mellitus	250		120	92	63	2·6	2·1	1·6	75·9	70·2	56·2
Other diseases of blood*	289		54	35	12	1·2	0·8	0·3	24·8	20·8	10·3
Epilepsy	345		56	40	40	1·2	0·9	1·0	41·8	34·5	36·7
Otitis media	381–2		64	57	32	1·4	1·3	0·8	9·2	4·7	1·4
Upper respiratory tract infections	460–5		124	63	75	2·7	1·5	1·9	12·8	12·8	10·2
Asthma	493		98	158	239	2·1	3·7	6·0	35·1	33·5	23·0
Hypertrophy of tonsils and adenoids	500	474	115	104	87	2·5	2·4	2·2	6·1	4·5	4·5
Appendicitis	540–2		615	368	194	13·4	8·6	4·9	71·8	53·7	38·1
Osteochondrosis	722	732	52	49	23	1·1	1·1	0·6	85·2	77·8	59·0
Congenital anomalies:	740–59		493	331	246	10·7	7·7	6·2	44·5	32·2	22·6
Of heart	746		23	3	5	0·5	0·1	0·1	71·9	50·0	33·3
Of genital organs	752		155	96	33	3·4	2·2	0·8	32·0	18·5	6·2
Of musculoskeletal system	754–6		156	113	97	3·4	2·6	2·4	70·9	82·1	59·5
Fracture of humerus	812		67	37	16	1·5	0·9	0·4	33·5	25·9	11·6
Fracture of femur	820–1		82	75	71	1·8	1·7	1·8	86·3	92·2	88·8
Head injury	850, 854		73	59	44	1·6	1·4	1·1	3·7	3·4	2·8
Burns	940–9		61	64	29	1·3	1·5	0·7	67·0	69·6	37·2

*The full ICD term is 'other diseases of blood and blood-forming organs' which includes mesenteric adenitis.

Table 3 Diagnoses which accounted for 1000 days or more in hospital in at least one year

Diagnosis	*ICD8 code*	*ICD9 code*	*Total No of days spent in hospital in aggregate each year by children with each diagnosis*		
			1975	*1979*	*1984*
Diarrhoeal disease	9		1113	122	139
Malignant neoplasms	140–203, 208–9		1005	438	211
Diabetes mellitus	250		2256	1242	762
Epilepsy	345		1055	900	818
Strabismus	373	378	1636	895	694
Otitis media	381–2		2069	2519	2679
Deafness	388–9	389	1170	1076	410
Upper respiratory tract infection	460–5		3583	1364	1804
Asthma	493		1535	2237	3956
Hypertrophy of tonsils and adenoids	500	474	5979	6378	5103
Appendicitis	540–2		6038	3975	2444
Redundant prepuce	605		787	894	1091
Osteochondrosis	722	732	1772	1419	447
Congenital anomalies:	740–59		10 055	7157	4604
Of heart	746		534	292	121
Of genital organs	752		2149	1848	1059
Of musculoskeletal system	754–6		4130	2483	1441
Fracture of humerus	812		1012	632	403
Fracture of femur	820–1		3246	2583	2245
Head injury	850, 854		3743	3032	2302
Burns	940–9		1544	969	544
Poisoning	960–89		1189	846	554

respiratory tract infections, hypertrophy of tonsils and adenoids, and head injury.

Thirdly, we calculated the total number of bed days used by patients with each diagnosis. Diagnoses that accounted for 1000 days or more in hospital in at least one year are shown in table 3. In 1975 the conditions that accounted for more than 3000 bed days were, in order of magnitude of use, congenital anomalies, appendicitis, hypertrophy of tonsils and adenoids (the diagnosis associated with tonsillectomy), congenital anomalies of the musculoskeletal system, head injury, upper respiratory tract infections, and fracture of the femur. In 1984 only three conditions accounted for over 3000 bed days: hypertrophy of tonsils and adenoids, congenital anomalies, and asthma. The number of bed days used declined over time for most conditions. As can be inferred from table 1, in some instances the decline partly represented a decline in numbers of children admitted (for example, diarrhoeal disease, malignant neoplasms). In other instances the main component of the decline was a fall in time spent in hospital per child admitted (for example, osteochondrosis, burns). For most conditions both factors contributed to the decline (for example, congenital anomalies of limbs).

Discussion

The data we have presented cover all clinical specialties (except mental handicap and mental illness) and therefore provide a profile of care that may not be readily apparent to doctors working with children in any one clinical specialty. Data are not available to the Oxford record linkage study about residents of the six districts who are treated outside the study area. Our data on population based rates therefore underestimate care received by children to the extent that they are treated elsewhere. Aggregated statistical returns used for financial resource allocation purposes show that about 5% of paediatric admissions for residents of the six district area occur outside it and that this has not changed appreciably over time. Notably, however, there is no regional specialist paediatric oncology centre in Oxford and our data underestimate to some extent numbers of bed days used by children with cancer.

Coding of data for the Oxford record linkage study is undertaken by coding clerks using clinical summaries and case notes completed by clinicians. The coding clerks are specially trained for this purpose and work in teams structured to provide supervision and peer review. In the period covered by this study completeness of coding was routinely checked.[9] Validation studies of the accuracy of coding were not routinely undertaken on a random sample but validation has been undertaken in a number of studies of particular clinical conditions by checking codes against the content of case notes, and coding has been found to be good.[10–12]

The quantification of clinical conditions responsible for substantial periods of time spent in hospital can be undertaken in a number of ways. First, conditions can be identified where the time spent in hospital *per child admitted* is relatively long. Time in hospital may be calculated per episode of admission or, where medical record linkage is available, it may be calculated as time spent in hospital per child per year. The duration of time spent in hospital may be calculated as means, modes, medians, or more detailed measures of the frequency distribution such as centiles. We selected the measure of medians partly for the simplicity of using a single measure and partly because means may be substantially influenced by small numbers of 'outlying' values. As a second main measure, we calculated the *number of 'long stay' children* with each condition. This identified not only conditions where median lengths of stay per child admitted were long but also those where medians were short but where there were none the less appreciable numbers of long stay patients. Third, we identified conditions where large *numbers of bed days* were used which in essence incorporates measures of the commonest reasons for hospital admission. It is reassuring that, in general, whichever measures were used, the amount of time spent in hospital by children declined over the years. Within this general decline, however, there are areas of increasing activity that reflect changes in prevalence, survival, and medical practice. For example, we have noted increased times spent in hospital by children with leukaemia and other malignant neoplasms: partly, this reflects increase in survival. In 1970, five year survival with Wilms' tumour was 55% but by 1980 was 75%; acute lymphoblastic leukaemia survival increased from 25% to 55% over the timespan.[13] In addition, the pattern of treatment has altered to involve more intensive chemotherapy given over shorter periods but with consequent longer periods of severe neutropenia. A direct result has been longer inpatient stays: at Birmingham Children's Hospital, for instance, bed occupancy for children with cancer increased from a mean of 11·8/day to 17·3/day between 1982 and 1986 with no significant change in the number of new patients treated.[13]

We also found increased time spent in hospital by children with congenital metabolic disorders, by far the commonest of which is cystic fibrosis. Purchasers and providers need to be aware of changes in the management of this condition which may have an impact on the frequency and length of stay for children in hospital. In a clinical budgeting exercise at Booth Hall Children's Hospital in 1983, particular note was made of a treatment policy, novel at the time, involving admissions every three months for a 14 day course of intravenous antibiotic. The effect of this was that an increase in a particular consultant's total number of admissions of just 1·8% in two years included a change in case mix *in favour* of cystic fibrosis leading to an increase in bed days of 27·2%.[14] However, planning is also bedevilled by the pace of change in technological innovation which now permits much of the intravenous treatment to take place at home.[15]

Hospital care for asthma has also increased. This has been widely documented by others.[16, 17] There is controversy as to the magnitude of any increase in asthma prevalence. The escalating numbers of such children admitted to hospitals throughout the UK may simply reflect a change in general practitioners' response to this condition. Any such change might be expected only to increase the number of 'short stay' asthmatics. However, our findings show that there was also an appreciable rise in those staying more than five days. This is likely to be related to an increase in severity and/or an increase in prevalence.

In planning how best to purchase and provide care for children, health authorities and provider units need information about volumes of clinical care, such as bed usage, and about changes in them in order to formulate and plan to meet their strategic and operational objectives.

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Congenital hypothyroidism detected by neonatal screening: relationship between biochemical severity and early clinical features

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Abstract

The relationships between biochemical severity of hypothyroidism (as judged by plasma thyroxine) and the clinical and radiographic findings at diagnosis were evaluated in 449 infants born in 1982–4 with congenital hypothyroidism identified by neonatal screening. Details of pregnancy, delivery, and the neonatal period were also examined and compared with the findings in a normal population of 36 727 infants born in 1988. Infants with plasma thyroxine values of 30 nmol/l or less had a significantly higher incidence of prolonged jaundice, feeding difficulties, lethargy, umbilical hernia and macroglossia, showed more severe delay of bone maturation on a knee radiograph, and had a higher proportion of thyroid agenesis on isotope scan. In contrast, an ectopic or hypoplastic gland was more common in infants with plasma thyroxine values above 30 nmol/l. Prevalence of illness in pregnancy and mode of delivery was not related to severity of hypothyroidism and were similar to figures for the normal population. Induction of labour, gestation over 40 weeks, and birth weight above 3500 g were significantly more common in the hypothyroid infants. Perinatal illness and congenital malformations were more common in the infants with low plasma thyroxine values at diagnosis.

Screening for congenital hypothyroidism started in the UK on a pilot basis in 1978; by mid-1982, after a recommendation by the Department of Health,[1] routine screening had been introduced throughout the country. The Medical Research Council (MRC) Register of Children with Congenital Hypothyroidism was set up to collect detailed information on the outcome in children born with congenital hypothyroidism during 1982–4. Information on incidence, deaths, congenital malformations, and ethnic background has already been published.[2]

It has now become clear that there is considerable variation in the biochemical severity of hypothyroidism in children detected by screening[3 4] and that this variation is closely related to the type of thyroid disorder which is present. In general, agenesis of the thyroid is associated with severe hypothyroidism, while ectopia, hypoplasia, or inherited defects of thyroid hormone synthesis are often associated with a less severe biochemical disturbance.[5–7] The present paper examines the relationship between biochemical severity (as judged by plasma thyroid hormone concentrations at diagnosis) and clinical features at diagnosis, early radiological findings (radiograph of the knee and isotope scan of the neck), pregnancy and perinatal events, and family history of thyroid disorder.

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Subjects and methods

SUBJECTS

At the beginning of 1990 the register held the names of 472 children born between 1982 and 1984 who had been diagnosed by neonatal screening. This number includes 14 children who have since died and 15 who have been lost to follow up because of emigration or other change of address. Excluded from the present study were 23 children (including one who died) in whom plasma thyroid hormone concentrations had not been measured before treatment, leaving 449 children (139 boys and 310 girls).

DATA COLLECTION AND STATISTICAL ANALYSES

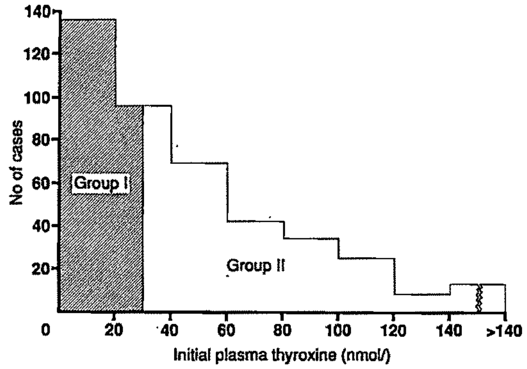
The paediatricians responsible for each child's clinical management were asked to provide details concerning pregnancy and birth, diagnosis, initiation of treatment, physical health, and family background. This information was recorded using a standard proforma which included a checklist of symptoms at the time of first clinical assessment (usually after a positive screening report) and requested the results of diagnostic tests, and of a radiograph of the knee and isotope scan of the neck (if performed).

Thyroid hormone concentrations at diagnosis had been measured either as total thyroxine (T_4) (n=372), free thyroxine (FT_4) (n=75) or triiodothyronine (T_3) (n=2). Before the start of treatment, 68 blood specimens were obtained from 58 children, each specimen was analysed for total thyroxine and free thyroxine, and from this analysis an equation was formulated:

$$\text{Log } T_4 = 2{\cdot}219 + 0{\cdot}9573 \times \text{Log } FT_4$$

Using this equation (S Tillotson, *et al*, personal communication), 55 definitive results for plasma free thyroxine were converted to total thyroxine values. The distribution of initial thyroxine values for 420 children are shown in the figure.

To examine the relationship between severity of hypothyroidism and other clinical variables it was decided to divide the children into two groups, group I with thyroxine values of 30 nmol/l or less and group II with values greater than 30 nmol/l. The value of 30 nmol/l was chosen as it divided the subjects into two roughly equal groups. A further seven children



Distribution of initial plasma thyroxine values in 420 of the 449 children with congenital hypothyroidism detected by screening. The number of cases with low thyroxine concentrations is underestimated in the figure as 27 subjects were not included because the initial result was reported as 'less than 25 nmol/l' or 'less than 30 nmol/l', or the free thyroxine as 'less than 2·5 nmol/l', and in two subjects plasma triiodothyronine concentrations were 0·5 and 0·7 nmol/l.

with thyroxine results reported as 'less than 25 nmol/l' or 'less than 30 nmol/l' and 20 with free thyroxine values reported as 'less than 2·5 nmol/l' were ascribed to group I, with two who had plasma triiodothyronine values of 0·5 and 0·7 nmol/l, bringing group I to 215 cases and group II 234 cases.

The relationships between biochemical severity and other factors were explored in a series of tables. As not all of the subjects had a complete range of observations the tables are based on different combinations of subjects. Data on initial symptoms are available for 447 subjects, radiographs of the knee and isotope scans of the neck were carried out in 260 and 179 subjects respectively. Details of antenatal progress were available in 449 subjects, whether or not induction was undertaken in 393, mode of delivery in 421, gestation length in 430, and birth weight in 418.

Table 1 Prevalence of individual symptoms of hypothyroidism at the time of diagnosis. Results are number (%)

	Group I (n=215)	*Group II (n=232)*
Features listed in questionnaire:		
Prolonged jaundice	128 (59)	77 (33)**
Feeding difficulty	75 (35)	36 (16)**
Lethargy	73 (34)	32 (14)**
Umbilical hernia	68 (32)	42 (18)*
Macroglossia	53 (25)	28 (12)*
Constipation	38 (18)	24 (10)
Cold or mottled skin	39 (18)	24 (10)
Hypothermia	6 (3)	7 (3)
No symptoms	34 (16)	78 (33)**
Other clinical features reported:		
Abnormal cry	16 (7)	15 (6)
Oedema	10 (5)	8 (3)
Hypothyroid appearance	12 (6)	6 (2)
Hypotonia	6 (3)	7 (3)

Group I and group II had initial plasma thyroxine concentrations ≤30 nmol/l or >30 nmol/l respectively.
Significance of difference between groups: **$p<0·001$, *$p<0·01$.

Table 2 Radiographic findings in the knee of 260 children with congenital hypothyroidism. Results are number (%)

Radiographic findings	*Group I (n=131)*	*Group II (n=129)*	*Total (n=260)*
Both epiphyses visible	35 (27)	72 (56)	107 (41)
Femoral epiphysis alone visible	25 (19)	38 (29)	63 (24)
Neither epiphysis visible	71 (54)	19 (15)	90 (35)

Group I and group II had initial plasma thyroxine concentrations ≤30 nmol/l or >30 nmol/l respectively.
Significance of difference between groups: $\chi^2=45·47$; $p<0·001$.

Prenatal and perinatal findings were compared with those in an unselected population of 36 727 infants born in the north west Thames region in 1988.[8]

Where appropriate, differences between groups I and II, and between the overall group of children with congenital hypothyroidism and the normal population, were assessed using χ^2 tests, taking a probability of less than 0·01 to indicate statistical significance.

Results

SYMPTOMS OF HYPOTHYROIDISM

The prevalence of symptoms (table 1), as defined by the checklist sent to paediatricians, was consistently greater in group I than in group II although the differences were only significant for the five most common symptoms. Jaundice for more than three weeks was the most commonly reported symptom, followed by feeding difficulty, lethargy, umbilical hernia, macroglossia, constipation, cold or mottled skin, and hypothermia. In group I 16% of the children had no symptoms compared with 33% in group II, whereas 13% of children in group I showed five or more symptoms compared with less than 2% in group II.

In 38 infants (25 group I; 13 group II) who had been suspected of having congenital hypothyroidism on clinical grounds before the screening result was known there was a significantly increased incidence of persistent jaundice (74%) and feeding difficulties (58%). Lethargy (37%), macroglossia (24%), umbilical hernia (21%), constipation (13%), or a cold mottled skin (13%) were no more common than in the group as a whole.

BONE AGE AND THYROID SCAN

In 260 children who underwent radiography of one knee at diagnosis (table 2), both epiphyses were absent in 54% of group I compared with 15% in group II. By contrast, both epiphyses were visible in 56% of group II, compared with only 27% in group I, a highly significant difference.

Only 179 infants had an isotope scan (table 3) and of these 40% showed an absent thyroid gland. However, in group I the proportion was 73% compared with only 12% in group II, whereas 61% of group II had an ectopic gland compared with only 15% in group I. A normally sited gland (indicating a probable defect of thyroid hormone synthesis) was present with approximately equal frequency (12% and 17%) in both groups of children. Hypoplastic or hemithyroid glands were reported in 10 infants all of whom had relatively mild hypothyroidism.

PREGNANCY AND DELIVERY

Sixty nine out of 447 mothers (15%) were reported as having some complication or illness during pregnancy (table 4), a prevalence very similar to that in the general population of the north west Thames region; 9% of mothers had hypertension or toxaemia, and 2% insulin dependent or gestational diabetes mellitus; 4% had a range of different illnesses. Some form of medication (other than iron and vitamin preparations) during pregnancy was taken by 15%, the most common being antibiotics (5%), antiemetics (3%), antihistamines (2%), or sedatives (1%); 19% reported smoking more than five cigarettes daily and 3% drank alcohol regularly while pregnant. There were no differences between groups I and II.

Mean maternal age at delivery was 27·1 years ($n=341$), compared with 28·0 years in the general population; mean paternal age was 30·3 years ($n=286$). The mode of delivery was very similar in groups I and II and in the general population. However, labour was induced in 53% of group I and 35% of group II, compared with 15% of the general population, a trend which is highly significant.

PERINATAL HISTORY

Overall, 44% of the hypothyroid children had birth weights above 3500 g as compared with 36% in the general population, a highly significant difference. However, there was no significant difference in birth weight distribution between group I and group II.

Problems at or after birth were reported in 25 hypothyroid infants (table 5), 16 in group I (7%) and nine in group II (4%). In 11 infants illness was associated with prematurity and in nine of them the birth weight was less than 2500 g. Thirty two children were recorded as having congenital anomalies (other than of the thyroid gland) when first assessed. Follow up revealed anomalies in another three patients, giving an overall incidence of 8%. Twenty six of these infants were in group I and nine were in group II ($p<0{\cdot}01$). Ten children in group I died before the age of 2 years, compared with three in group II.

Table 3 Thyroid scan findings in the 179 cases of congenital hypothyroidism. Results are number (%)

Thyroid scan result	Group I (n=84)	Group II (n=95)	Total (n=179)
Absent thyroid	61 (73)	11 (12)	72 (40)
Normally sited gland	10 (12)	16 (17)	26 (15)
Ectopic gland	13 (15)	58 (61)	71 (40)
Hypoplastic gland or hemithyroid	0	10 (11)	10 (6)

Group I and group II had initial plasma thyroxine concentrations ≤ 30 nmol/l or >30 nmol/l respectively.
Significance of difference between groups: $\chi^2=72{\cdot}31$; $p<0{\cdot}001$.

Table 4 Pregnancy and perinatal data in 449 children with congenital hypothyroidism compared with the normal population in the region. Results are number (%)

Variable	Group I	Group II	Normal population
Illness in pregnancy:			
Hypertension-toxaemia	15/215 (7)	24/234 (10)	3612/28450 (13)
Diabetes	3/215 (1)	7/234 (3)	484/36542 (1)
Other	7/215 (3)	13/234 (6)	
Other pregnancy factors:			
Medication	31/215 (14)	38/234 (16)	
Smoking	33/184 (18)	36/189 (19)	8168/36656 (22)
Alcohol	4/164 (2)	5/173 (3)	
Induction of labour	102/194 (53)**	69/199 (35)†	5542/36646 (15)
Mode of delivery:			
Normal	145/203 (71)	156/218 (71)	28916/37612 (77)
Assisted	31/203 (15)	26/218 (12)	3719/37612 (10)
Breech	4/203 (2)	4/218 (2)	463/37612 (1)
Caesarean section	23/203 (11)	32/218 (15)	4514/37612 (12)
Gestation:			
Below 37 weeks	20/209 (10)	11/221 (5)	2391/36653 (7)
Over 40 weeks	100/209 (48)	94/221 (42)†	6983/36653 (19)
Birthweight:			
Below 2500 g	20/203 (10)	14/215 (6)	2679/37593 (7)
Above 3500 g	86/203 (42)	100/215 (46)†	13684/37593 (36)

Group I and group II had initial plasma thyroxine concentrations ≤ 30 nmol/l or >30 nmol/l respectively.
Significance of difference between groups: **$p<0{\cdot}001$ and between all hypothyroid subjects and normal population: †$p<0{\cdot}001$.

Table 5 Perinatal illness, congenital malformations, and deaths in 449 children with congenital hypothyroidism

	Group I (n=215)	Group II (n=234)
Perinatal illness	16*	9
Birth asphyxia	3	2
Respiratory distress syndrome	1	4
Pneumonia/aspiration	4	2
Septicaemia/necrotising enterocolitis	6	0
Hypoglycaemia	1	1
Hypocalcaemia	1	0
Congenital malformations	26*	9
Deaths	10	3

Group I and group II had initial plasma thyroxine concentrations ≤ 30 nmol/l or >30 nmol/l respectively.
Significance of difference between groups: *$p<0{\cdot}01$.

FAMILY HISTORY OF THYROID DISEASE

By the end of 1989, 15 children (3%) (including two pairs of twins) had a sibling with congenital hypothyroidism. Of the four who had thyroid scans, three (including one pair of twins) had a normal or enlarged gland, indicating probable dyshormonogenesis. As thyroid scans were carried out on less than half the patients only 153 children with dysgenesis of the thyroid have been identified. These children have a total of 214 siblings, only one of whom has congenital hypothyroidism. Two girls with congenital hypothyroidism are maternal cousins and an isotope scan in one of them showed no evidence of thyroid tissue.

Thyroid disease was reported in 13 mothers (3%); five had goitres, three thyroglossal cysts, two hypothyroidism, and three hyperthyroidism.

Discussion

One of the most striking features of congenital hypothyroidism to have emerged since the introduction of neonatal screening is a very wide range in biochemical severity at the time of diagnosis.[2 3] Screening has allowed early identification of children with mild as well as severe forms of the disorder and this probably accounts for the apparent increase in the incidence of congenital hypothyroidism noted when screening first began, along with a considerable decline in the frequency of 'juvenile hypothyroidism' presenting during later childhood. In the present study 46 subjects (10%) had normal plasma thyroxine values at the time of diagnosis, and while it remains possible that a few of these children may still prove to have normal thyroid function, most (89%) have been shown to have raised values of thyroid stimulating hormone either on treatment or after its temporary withdrawal.

In the present study there was a close relationship between the biochemical severity of hypothyroidism and clinical symptoms. Infants with plasma thyroxine concentrations below 30 nmol/l were much more likely to show prolonged jaundice, feeding difficulties, lethargy, umbilical hernia, and macroglossia than those with a less appreciable reduction in thyroxine values. Others have shown that such symptoms can also be used to differentiate hypothyroid infants from those with false positive screening results. In an important study from Finland, Virtanen compared the clinical findings at the age of 6 days in 95 newborn infants with hypothyroidism and 450 infants with false positive screening test results.[9] Jaundice, macroglossia, and hypothyroid appearance, abdominal distension, umbilical hernia, and cold skin were very much more common in the hypothyroid group, as were prolonged gestation, high birth weight, an above average head circumference, and a good Apgar score. In a smaller study, Rochiccioli *et al* found that the presence of macroglossia, umbilical hernia, hypothyroid appearance, cold mottled skin, and a wide posterior fontanelle could be used to separate hypothyroid infants from those with false positive screening tests.[5] Nevertheless, it should be noted that in the present study 16% of the infants with severe hypothyroidism were symptom free at the time of detection.

As has been reported previously,[3–5] biochemical severity was closely related to bone age. There is also evidence suggesting that the degree of bone age retardation may be of prognostic value with respect to later intelligence.[10–13]

A relationship between thyroid scan results and the early biochemical findings is well recognised.[5–7] In the present study, the thyroid scan findings were more closely related to severity of hypothyroidism than any other factors. Of those who were scanned, 40% showed agenesis of the gland and 85% of these had plasma thyroxine values of 30 nmol/l or less; 46% had an ectopic, hypoplastic, or hemithyroid and only 16% of these showed a comparable reduction in plasma thyroxine values, illustrating the close association between agenesis and severe biochemical disease. Estimates of the prevalence of agenesis of the thyroid in series from other countries have varied from 15% to 51% but some of this variation may be due to different sensitivities in the scanning technique. The scan results described above suggest a prevalence of thyroid hormone biosynthetic defects of 15% in the UK, similar to that found in France and Finland (13%).[5,14] This is a little lower than reported from North America (20–22%)[4,7] and higher than in Switzerland (6%).[15]

Although our study failed to identify any differences in maternal factors during pregnancy or in the mode of delivery between infants with congenital hypothyroidism and the general population, there was a striking increase in the frequency of induced labour and higher frequencies of postmaturity and infants with birth weights over 3500 g. The increased prevalence of postmaturity is a well recognised feature of congenital hypothyroidism,[4,16,17] although its significance with respect to the physiology of labour is still uncertain. A number of authors have also reported increased birth weight as a feature of congenital hypothyroidism.[11,16,17]

As reported previously,[2,18–20] congenital hypothyroidism is associated with an increased prevalence of other congenital anomalies, and almost 8% of the present sample had major malformations, compared with an expected frequency of 2–3%. The data suggest that some teratogenic factor is operating during early pregnancy but our study failed to identify any such factor other than the hypothyroidism itself.

This paper forms a report for the steering committee for the Medical Research Council's register of children with congenital hypothyroidism (Chairman Professor J A Davis).

We thank all the paediatricians across the country who have responded to our questionnaires and provided the data which make up this report. The study was supported by a project grant from the Medical Research Council.

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Relationship between urinary and serum growth hormone and pubertal status

E C Crowne, W H B Wallace, S M Shalet, G M Addison, D A Price

Abstract

Urinary growth hormone (uGH) excretion and serum growth hormone concentrations have been compared in three groups of children. Group 1 consisted of 21 children who had had cranial irradiation as part of their treatment for acute lymphoblastic leukaemia; group 2, 18 normal children; and group 3, 12 boys with constitutional delay in growth and puberty who were in early puberty. Children in groups 1 and 2 each had a 24 hour serum growth hormone profile (sampling every 20 minutes) and concurrent urine collection. The 12 boys in group 3 had a total of 21 profiles (sampling every 15 minutes for 12 hours) and concurrent urine collections.

In the prepubertal children (n=17), in both groups 1 and 2, there was a significant correlation between mean serum growth hormone and total uGHng/g creatinine. There were also significant correlations between total uGHng/g creatinine and both peak serum growth hormone and mean amplitude of the pulses in the growth hormone profile. In the pubertal children (n=22), in groups 1 and 2, whether combined or in separate groups, there was no significant correlation between total uGHng/g creatinine and mean serum growth hormone, peak serum growth hormone, or mean amplitude of the pulses in the growth hormone profile. In group 3 there were significant correlations between total uGHng/g creatinine and both the mean serum growth hormone and mean amplitude of the pulses in the profile. Therefore uGH estimations appear to correlate well with serum growth hormone profiles in children who are prepubertal or in early puberty, but not in those further advanced in pubertal development. These results may reflect a variation in the renal handling of growth hormone during pubertal development. uGH estimation may be an unreliable screening investigation for growth hormone insufficiency in mid to late puberty.

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The diversity of tests of growth hormone secretion in clinical use indicates the absence of an ideal test of growth hormone secretion. In clinical practice pharmacological stimulation tests such as insulin, arginine, or glucagon with an arbitrarily assigned 'normal' cut off value have been used to identify growth hormone deficient children. These tests do not provide information about physiological growth hormone secretion, and 24 hour serum growth hormone profiles for the assessment of physiological growth hormone secretion have obvious drawbacks in terms of invasiveness and cost. Hence the interest in estimation of urinary excretion of growth hormone as a non-invasive, easily performed test. Growth hormone assays have now attained the sensitivity required to detect the minute amounts of the hormone excreted in the urine,[1–3] and their use is being advocated as a means of screening for growth hormone deficiency.[4]

Abnormalities in growth hormone secretion in children and adults who have had cranial irradiation as part of their treatment for malignancies are well established.[5–8] Abnormalities ranged from growth hormone deficiency defined by classical criteria,[9] neurosecretory dysfunction with normal growth hormone responses to pharmacological tests but subnormal physiological growth hormone secretion,[7] and a failure of the puberty associated rise in spontaneous growth hormone secretion.[8] Children who have had cranial irradiation are therefore a particular group in whom screening tests of growth hormone need to be reliable enough to detect subtle changes in physiological growth hormone secretion.

Other categories of children frequently seen in a paediatric growth clinic include those with constitutional delay in growth and puberty (CDGP) or familial short stature. A simple, easily performed non-invasive means of assessing growth hormone secretion in such individuals would be very helpful.

In this study we have therefore compared urinary growth hormone (uGH) estimations and serum growth hormone profiles in three groups of children: normal children, children who have had low dose cranial irradiation as part of their treatment for acute lymphoblastic leukaemia (ALL), and boys with CDGP.

Patients and methods

GROUP 1: AFTER CRANIAL IRRADIATION

Twenty one children, aged 6·9–18·2 years (nine girls, 12 boys) who had received prophylactic cranial irradiation during treatment for ALL were studied. Nineteen received 18 Gy in 10 fractions over 14 days and two received 24 Gy in 10 fractions over 14 days. All 21 had received chemotherapy according to standard UK protocols, were in first remission, and a mean (SD) 6·4 (1·9) years from radiotherapy.

GROUP 2: NORMAL CHILDREN

Eighteen normal children, aged 3·8–18·9 years (six girls, 12 boys) were studied. Ten were normal siblings of group 1 and eight were children under investigation for genetic short stature (height velocity normal and normal growth hormone response to pharmacological stimulation tests but with a mid-parental height less than the 10th centile and a standing height more than 2 SD below the mean).

GROUP 3: CDGP

Twelve boys under investigation for CDGP were studied. They had a total of 21 profiles with concurrent urine collections before and after treatment with either low dose testosterone, oxandrolone, or placebo. Only six of the profiles were performed while the boys were actively receiving either oxandrolone (n=2) or testosterone (n=4).

The groups were further subdivided by pubertal stage according to the method of Tanner and Whitehouse.[10] Children in groups 1 and 2 each had a 24 hour growth hormone profile sampling every 20 minutes with concurrent urine collection (0900–0900 hours). Group 3 boys had an overnight 12 hour profile on each occasion (2000–0800 hours), with sampling every 15 minutes and a concurrent urine collection. Details of the children at the time of the profile are shown in table 1.

All the studies were approved by the local ethical committee and informed consent was obtained from the children and their parents.

ASSAYS

Serum growth hormone profiles were assayed in one batch using a standard diagnostic immunoradiometric assay (IRMA) kit (Netria, St Bartholomew's Hospital, London), and international reference standards. Urine samples were collected in polythene bottles kept at 4°C during the collection. Urine volumes were then measured and aliquots stored at −40°C in 0·1% bovine serum albumin and 0·1% azide solution until assayed, when aliquots were first dialysed against a phosphate buffer for 24 hours at 4°C. Growth hormone concentration was measured by a two step IRMA using 1·5 ml of dialysed urine. The first step consisted of a 24 hour incubation with 100 μl of ^{125}I labelled mouse monoclonal antihuman growth hormone antibody, and the second a 24 hour incubation with 100 μl of sheep polyclonal antigrowth hormone antibody coupled to a solid phase (antibodies obtained from Netria). Both incubations were at 4°C. Sensitivity was 0·8 pg/ml, intra-assay coefficients of variation were 2·0–8·1%, and interassay coefficients of variation 6·6–8·4%.[11]

Urinary creatinine estimations were performed by the standard Jaffé kinetic method.

CALCULATIONS AND STATISTICS

Results are expressed as mean (SD). Results of uGH (22 pg/ml=1 μmol/l) are expressed as ng per gram of creatinine to avoid inaccuracies due to incomplete or inaccurate urine collections and to allow comparison with published reports. Growth hormone profiles were analysed using the Pulsar Peak Detection Programme.[12] Correlations and regressions were calculated by standard least squares. Differences between groups were analysed using the Mann-Whitney U test. The significance of regression lines was calculated using Student's unpaired *t* test, the significance of the difference between regression lines calculated using a method of weighting.[13]

Results

There were no significant differences in mean peak and total concentrations of serum growth hormone within group 2, that is between the normal siblings and those under investigation for genetic short stature. In group 1, there was no significant difference in time since cranial irradiation between the prepubertal and pubertal children (6·6 (1·8) *v* 6·5 (1·7) years) but there was a significant difference in age at cranial irradiation between the prepubertal and pubertal children (3·8 (2·1) *v* 7·5 (3·0) years, $p<0{\cdot}05$).

RELATIONSHIP BETWEEN SERUM GROWTH HORMONE PROFILES AND uGH EXCRETION IN PREPUBERTAL CHILDREN (FIG 1)

There was a significant correlation between mean serum growth hormone and total uGHng/g

Table 1 Age and pubertal stage at the time of profile. Results are mean (SD)

Group	*Age at study*	*Pubertal stage*	*Time since treatment*	*Age at treatment*
1: ALL (after irradiation)				
Prepubertal (n=7)	9·6 (1·8)	—	6·6 (1·8)	3·8 (2·1)
Pubertal (n=14)	14·1 (2·0)	TV 5–12 ml (n=3), TV 25 ml (n=3); B3–B4 (n=2), B5 (n=6)	6·5 (1·7)	7·3 (3·1)
2: Normal children				
Prepubertal (n=10)	8·7 (2·4)	—	—	—
Pubertal (n=8)	15·3 (2·6)	TV 5–12 ml (n=3), TV 25 ml (n=3); B3 (n=1), B5 (n=1)	—	—
3: CDGP (n=21)	14·5 (0·9)	TV 4–6 ml (n=14), TV 8–12 ml (n=7)		

TV=testicular volume, B=breast stage.

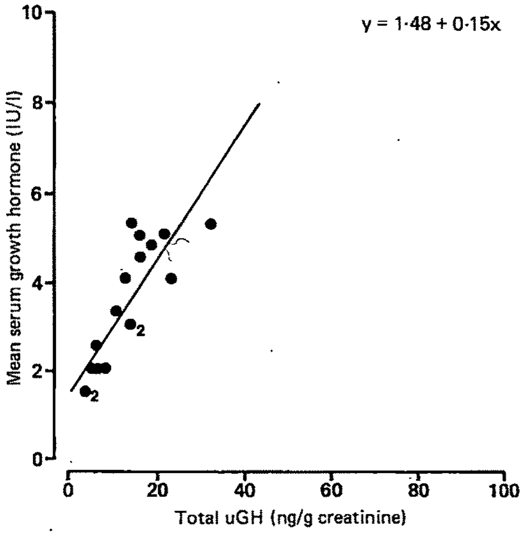

Figure 1 Relationship between total uGH excretion and mean serum growth hormone concentrations in 17 prepubertal children. Conversion factor for growth hormone: 2 IU/l= 1 μg/l.

creatinine in the prepubertal children ($r=0{\cdot}82$; $p<0{\cdot}001$). The relationship was described by the regression equation $y=1{\cdot}48+0{\cdot}15x$ (fig 1). The correlation between these two parameters was also significant in groups 1 and 2 taken separately ($r=0{\cdot}88$, $p=0{\cdot}009$; $r=0{\cdot}84$, $p=0{\cdot}003$ respectively), and there was no significant difference in the regression equations between the two groups. There were also significant correlations in the prepubertal children between total uGHng/g creatinine and both peak growth hormone in the growth hormone profile ($r=0{\cdot}86$, $p<0{\cdot}001$) and mean pulse amplitude in the growth hormone profile ($r=0{\cdot}71$, $p=0{\cdot}002$).

RELATIONSHIP BETWEEN SERUM GROWTH HORMONE PROFILE AND uGH EXCRETION IN BOYS WITH CDGP IN EARLY PUBERTY

There were significant correlations between total uGHng/g creatinine and both mean serum growth hormone ($r=0{\cdot}74$, $p<0{\cdot}001$) and mean amplitude of the growth hormone pulses in the 12 hour profile ($r=0{\cdot}4$, $p=0{\cdot}05$) in these boys. There was, however, no significant correlation between the total uGH excreted and the peak growth hormone in the profile ($r=0{\cdot}4$, $p=0{\cdot}12$).

RELATIONSHIP BETWEEN SERUM GROWTH HORMONE PROFILES AND uGH EXCRETION IN PUBERTAL CHILDREN (FIG 2)

The relationship between mean serum growth hormone and total uGHng/g creatinine was not significant in the pubertal children ($r=-0{\cdot}26$, $p=0{\cdot}24$) as seen in fig 2. The regression equation ($y=4{\cdot}84-0{\cdot}03x$) was significantly different to that of the prepubertal group ($p<0{\cdot}001$) but not significantly different from zero. The correlation between these two parameters was also not significant in either group 1 or 2 taken separately ($r=-0{\cdot}02$, $p=1{\cdot}0$; $r=-0{\cdot}4$, $p=0{\cdot}22$ respectively). Nor was there a significant correlation between these parameters in the boys and girls taken separately ($r=0{\cdot}2$, $p=0{\cdot}60$; $r=-0{\cdot}6$, $p=0{\cdot}1$ respectively). In addition, there were no significant correlations in the pubertal group between total uGHng/g creatinine and either peak growth hormone in the growth hormone profile ($r=-0{\cdot}29$, $p=0{\cdot}2$) or mean amplitude of the growth hormone pulses in the growth hormone profile ($r=-0{\cdot}34$, $p=0{\cdot}2$). Expressing uGH excretion as a uGH/g creatinine ratio or as total uGH (pg) did not alter these results. The six pubertal boys in groups 1 and 2 with testicular volumes less than 12 ml (that is, at a similar pubertal stage to the boys in group 3) did, however, show a significant correlation between total uGHng/g creatinine and both mean serum growth hormone and mean amplitude of the growth hormone pulses ($r=0{\cdot}74$, $p=0{\cdot}09$; $r=0{\cdot}72$, $p=0{\cdot}01$ respectively) when analysed separately.

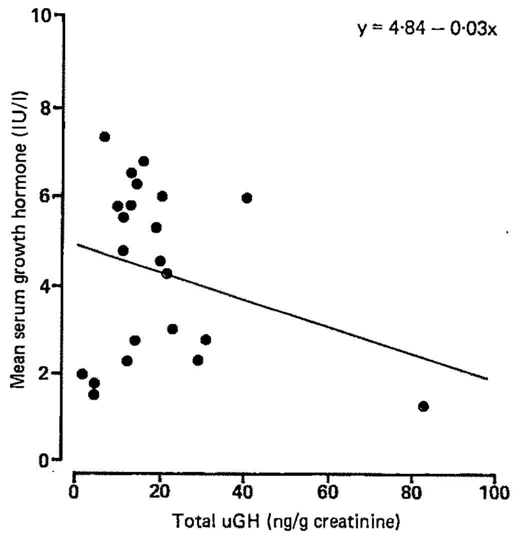

Figure 2 Relationship between total uGH excretion and mean serum growth hormone concentrations in 22 pubertal children. Conversion factor for growth hormone: 2 IU/l= 1 µg/l.

Table 2 Factors affecting renal function in the 21 children treated for ALL

Patient No	*Intravenous pyelogram at diagnosis*	*Nephrotoxic drugs*	*Renal function**
		Prepubertal	
1	Normal	Amikacin	N
2	Normal	Amikacin	T
4	Normal	—	N
6	Normal	Gentamicin	T
7	Normal	Amikacin	N
12	Normal	—	N
16	Normal	Netilmicin	T
		Pubertal	
3	Normal	Gentamicin, amikacin	T
5	Normal	Amikacin	N
8	Normal	—	N
9	Normal	Amikacin	N
10	Not performed	Amikacin	T
11	Normal	Gentamicin, and amikacin	T
13	Normal	—	N
14	Normal	Netilmicin, amikacin	T
15	Leukaemic infiltration	Gentamicin	N
17	Normal	Amikacin	N
18	Normal	—	N
19	Normal	—	N
20	Leukaemic infiltration	Netilmicin	T
21	Normal	—	N

*Renal function: N=normal blood urea and creatinine concentration, T=transiently raised concentrations during treatment, subsequently normal.

RENAL FUNCTION

All the children studied had normal plasma urea and creatinine concentrations. In particular the group with ALL had normal renal function after their chemotherapy. Factors during the course of their treatment affecting renal function are shown in table 2.

All the children except one had an intravenous pyelogram at diagnosis. Two showed evidence of leukaemic infiltration. The children all received chemotherapy according to standard protocols and these did not include known nephrotoxic drugs. During their treatment, however, 14 children received antibiotics known to be nephrotoxic for treatment of intercurrent infections while immunosuppressed. Five were in the prepubertal group and nine in the pubertal group. All have subsequently had normal renal function tests, although during treatment eight children had plasma urea and creatinine concentrations transiently raised above age related normal values; three were from the prepubertal group and five from the pubertal group.

Discussion

Growth hormone excreted into the urine represents less than 0·002% of serum concentrations,[14] and is the end product of renal metabolism including glomerular filtration, followed by extensive tubular reabsorption, and lysosomal hydrolysis. The rate limiting step under normal conditions is the filtration process as neither tubular reabsorption nor intracellular hydrolysis is saturated.[15] Endogenous growth hormone production has been shown to increase in puberty by an amplitude modulated process.[16] Furthermore, renal excretion of uGH increases in spontaneous puberty[14,17] and after the treatment of delayed puberty with testosterone.[14] Glomerular filtration rate, however, also increases in puberty, although changes in tubular function have not been described. Therefore our results showing a loss of the relationship between serum growth hormone and uGH during puberty are not totally unexpected in view of the changes in a number of important variables. The fact that our boys with CDGP showed a significant correlation between uGH excretion and serum growth hormone concentrations is interesting but not contradictory. Growth hormone concentrations in early puberty do not differ significantly from those in prepubertal boys[16] and the majority of this group were in early puberty. Unfortunately the mean values shown in table 3 are not directly comparable as groups 1 and 2 had 24 hour profiles and urine collections in group 3 boys had 12 hour studies. The mean total concentrations in group 3 are likely to be higher than those of groups 1 and 2 as they do not include daytime growth hormone secretion when less growth hormone is produced.

Significant correlations between uGH excretion and both the growth hormone response to provocative tests[18,19] and the mean serum growth hormone concentrations during profiles in diabetic and normal children,[17] normal, short statured and growth hormone deficient children,[20] and normal and short statured adults[21] have been described. Okuna *et al* investigated prepubertal children only,[20] and Weissberger *et al* studied adults, patients with acromegaly, and only 12 short children, whose pubertal stage was not specified.[21] Edge *et al* analysed changes in uGH excretion during puberty but did not state the pubertal status of the children undergoing growth hormone profiles.[17] Therefore the significant correlation found in the latter group may reflect a majority of prepubertal and early pubertal children (age range 5·9–15·9 years).[17]

Table 3 Relationship between mean serum growth hormone and total uGHng/g creatinine. Results are mean (SD)

Group	*No of children*	*Mean serum growth hormone (IU/l)**	*Total uGH (ng/g creatinine)*	*r*	*p Value*
Prepubertal (24 hour profile):					
Total	17	3·5 (1·4)	13·1 (7·6)	0·82	<0·001
Normal	10	3·6 (1·3)	12·7 (5·3)	0·84	0·003
ALL	7	3·2 (1·6)	13·8 (10·5)	0·88	0·009
Pubertal 24 hour profile):					
Total	22	4·3 (2·0)	18·8 (16·9)	−0·26	NS
Normal	8	5·2 (2·0)	17·0 (12·6)	−0·02	NS
ALL	14	3·8 (1·8)	19·7 (19·4)	−0·40	NS
CDGP (12 hour profile):					
	21	7·3 (5·1)	19·9 (17·3)	0·74	<0·001

*Conversion factor for growth hormone: 2 IU/l=1 μg/l.

In adults single overnight uGH measurements were found not to discriminate completely between those with acromegaly and normal controls,[22] nor was there a significant correlation between uGH excretion and serum growth hormone concentrations in the adults with active acromegaly.[21] This may be due to changes in renal function caused by growth hormone itself.[23] In addition, within an individual, significant day to day variability in uGH excretion of the order of 30% has been described.[24] The latter is most probably due to changes in renal function. The lack of any correlation between the dose of growth hormone injected and amount of uGH measured in the urine in growth hormone insufficient children[14] provides further evidence for the individual variability of growth hormone handling. Furthermore, the excretion of uGH increases in renal failure and diabetic children regardless of changes in growth hormone secretion,[17,25] but it is not significantly correlated with the excretion of other urinary proteins[26] thereby underlining the importance of variations of renal function on uGH excretion.

Group 1 (ALL) would have been at particular risk of incurring renal damage either as a result of their original disease or in the course of its treatment. Although there is no evidence of overt renal problems in the ALL children studied, they could have incurred sufficient tubular damage during treatment to affect renal handling of growth hormone. The fact that the prepubertal children with ALL were not significantly different from the normal prepubertal children in their excretion of uGH, however, argues against significant tubular damage affecting uGH excretion in these children. There was no difference in treatment, clinical course, or time elapsed since treatment between the prepubertal and pubertal irradiated children, although the children who were pubertal at the time of study were significantly older when originally treated than the prepubertal children (7·3 (3·1) *v* 3·8 (2·1) years, $p<0{\cdot}05$). If anything this should render them less vulnerable, as young children are more susceptible to permanent kidney damage from insults such as urinary tract infections. These observations counter the suggestion that tubular damage in group 1 disrupted uGH excretion. Furthermore the absence of a relationship between uGH excretion and serum concentrations in the normal pubertal group cannot be explained by renal pathology.

In conclusion, further investigation of the impact of both physiological and pathological changes in renal function on uGH excretion are necessary to determine the reliability of uGH as a screening test for growth hormone deficiency. Estimation of uGH does not appear to reflect serum growth hormone concentrations reliably in mid to late puberty and thus is not an appropriate screening test for growth hormone deficiency during puberty. Careful measurement of growth and the more traditional methods of growth hormone assessment remain essential.

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Limited joint mobility in subjects with insulin dependent diabetes mellitus: relationship with eye and kidney complications

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Abstract

Three hundred and fifty seven subjects (178 males and 179 females) with insulin dependent diabetes mellitus were evaluated for the presence of limited joint mobility of the interphalangeal joints. Sixty six subjects (19%) had stage 1 and 26 subjects (7%) had stage 2 involvement of their interphalangeal joints. The presence of contractures was significantly related to mean longitudinal glycated haemoglobin (HbA_1) concentrations, duration of diabetes, age of onset, mean longitudinal cholesterol concentrations and blood pressure. Limited joint mobility was also significantly associated with early diabetic retinopathy and raised albumin excretion rates. Limited joint mobility remained a significant factor in the logistic regression model for albuminuria and grade of retinopathy when controlled for smoking, cholesterol concentrations, duration of diabetes, age, gender, and blood pressure. However, limited joint mobility was only significantly associated with diabetic retinopathy when the effect of HbA_1 concentrations was included in the multivariate model.

Diabetes mellitus is the leading cause of new cases of blindness from the ages of 20–74 years[1 2] and the number one cause of new cases of dialysis is adults[3] in the US. Poor metabolic control,[4] duration of diabetes, high normal blood pressure,[5 6] and smoking[7] have been shown to be associated with early diabetic retinopathy and/or early renal damage.

Limited joint mobility has been observed with variable prevalence (8·4%–46%) in subjects with insulin dependent diabetes.[8 9] These contractures may involve the hands, feet, and larger joints. Thickening of the skin (waxy appearance) had also been associated with limited joint mobility.[10] An increased risk for diabetic microvascular complications in subjects with limited joint mobility has also been described.[10] The increased prevalence of microvascular complications in subjects with limited joint mobility may be partly due to other associated factors. Previous reports have not used multivariate statistical models such as logistic regression to control for the effects of longitudinal glycated haemoglobin (HbA_1) concentrations, duration of diabetes, smoking, blood pressure levels, and other confounding variables when analysing the data for an association of limited joint mobility with early diabetic retinopathy and/or renal damage.

The purpose of this study was to evaluate the relationship of limited joint mobility with early diabetic renal and retinal damage. The influences of other factors were controlled using logistic regression models.

Subjects and methods

Three hundred and fifty seven subjects (178 males and 179 females) with insulin dependent diabetes who were at least 14 years old and who had had diabetes for at least five years were evaluated for renal and retinal changes in our eye-kidney clinic. The eye-kidney clinic began in 1986 and after their initial evaluation, subjects were asked to return at least once a year. Subjects were included in this report only if they had brought in a minimum of two overnight timed urine samples for microalbumin determinations. There were no other exclusion criteria for the study. Approximately 95% of eligible subjects from our diabetic clinic have been evaluated in the eye-kidney clinic.

During routine physical examination, each subject was asked to approximate the palmar surfaces of the interphalangeal joints of both hands with fingers extended. Normal approximation at the interphalangeal joints is usually a minimum of 180°. Subjects are designated by numbers of fingers with interphalangeal joint contractures as stage 0 (no limitation), stage 1 (one interphalangeal joint involved in both hands), or stage 2 (two or more interphalangeal joints involved with or without one large joint involvement).

All subjects had direct ophthalmoscopy (with pupils dilated) by at least two examiners (one ophthalmologic, and one paediatric) followed by colour retinal photographs, intravenous fluorescein angiograms and a slit lamp examination during their initial visit to the eye-kidney clinic. Subsequent visits included repeating all measurements except fluorescein angiography. Retinal findings were graded using a modified Airlie House classification of diabetic retinopathy.[11 12] Subjects were classified into three groups based on the eye findings of the worst eye (grade 1: no retinal change, grade 2: microaneurysms only, and grades 3 to 6: more advanced retinopathy). The retinal specialist made the final grading with no knowledge of previous eye grades, joint contractures, glycaemic control, smoking status, blood pressure, or albumin excretion rate values, so that the grading was done in a masked fashion.

Timed overnight urine samples were collected for albumin excretion rate (AER) determinations as previously described.[4 13] Albumin concentrations were determined by radioimmunoassay (albumin double-antibody kit, Diagnostic Products Corporation). The subjects with or without limited joint mobility were then classified into three groups based on their overnight AER: (i) normal, less than 7·6 μg/min, (ii) borderline, 7·6–30·0 μg/min or, (iii) abnormal, over 30 μg/min. The accuracy of microalbumin concentrations at the lower limit was improved by routinely including a 2·5 mg/l standard in the samples for the standard curve. The AER detection limit by this method in our laboratory is 0·5 μg/min, our interassay and intra-assay coefficients of variation are 1·7–4·4% and 3·6–7·4%, respectively.[13]

Serial HbA$_1$ values for all subjects were determined using ion exchange resin,[4] (Isolab fast haemoglobin test system, Isolab Inc) with normal concentrations of 6·3 to 8·2%. The normal values for HbA$_1$ have remained in this range since 1979. A mean of 7·6 years of HbA$_1$ concentrations were available for each subject and for the purposes of this study a mean of all values ever recorded was used for data analyses. Serum cholesterol was measured by enzymatic assay using the Cobas autoanalyser and Beckman reagents.

Blood pressure was measured at each visit as previously described.[7] Subjects were considered to have a 'high normal' systolic and/or diastolic blood pressure if levels above the 90th centile for age were detected on at least two separate clinic visits and were lower than 141/90 mm Hg, the level defining hypertension. All subjects signed a consent form approved by the University of Colorado Health Sciences Center human subjects commitee. Smoking was defined as previously described.[9]

STATISTICAL METHODS

Statistical analyses included use of χ^2 test, Pearson correlation coefficients, and analysis of variance. When significant differences were found using analysis of variance, Dunnett's multiple *t* test was used to compare individual groups.

Multinomial logistic regression for ordinal response variables (also called proportional odds model) was used to assess the influence of limited joint mobility on diabetic retinopathy (grade 1, 2 and 3–6) and raised AER (normal, borderline, and abnormal) with and without the presence of other factors such as age, sex, duration of diabetes, HbA$_1$ concentrations, smoking, cholesterol concentrations, and blood pressure. A multinomial logistic regression was also used to assess the influence of the above factors on limited joint mobility.

Results

Limited joint mobility was present in 26% of the subjects (table 1). The subjects were classified into the three groups depending on the presence and stage of limited joint mobility. The mean (SEM) ages for subjects in the three groups were similar (table 1). The age ranges for the three groups, stages 0, 1, and 2, were 14 to 30, 14 to 34, and 14 to 34 years, respectively. The mean (SEM) duration of diabetes was 10·5 (0·2), 14·0 (0·6), and 14·0 (0·8) years for subjects with stages 0, 1, and 2, respectively ($p<0·001$, analysis of variance). Sex distribution was not significantly different for subjects with or without limited joint mobility ($p=0·08$, χ^2 test), although a tendency for more males having limited joint mobility was observed (table 1). Tobacco consumption and mean systolic blood pressure were not different between the three groups. Cholesterol concentrations were significantly different ($p=0·024$, analysis of variance) for the three groups (table 1). Limited joint mobility was significantly associated with mean HbA$_1$ concentrations (table 1). Mean HbA$_1$ concentrations were significantly higher in subjects with grade 2 limited joint mobility than subjects without limited joint mobility (Dunnett's multiple *t* test).

Mean diastolic blood pressures were also significantly different between the three groups ($p=0·005$, analysis of variance, table 1). When individual comparisons were made, only subjects with stage 2 limited joint mobility had significantly different levels from subjects without limited joint mobility. Hypertension was detected in seven subjects and was similarly distributed in the three groups. High normal blood pressure was observed in 14% (37/265) with stage 0, in 14% (9/66) with stage 1, and in 47% (12/26) with stage 2 limited joint mobility. A significant difference was observed in the frequency of high normal blood presssure among the three groups, especially in subjects with stage 2 limited joint mobility ($p=0·01$, χ^2 test).

Using actual values the joint classification correlated significantly with the AER ($r=0·31$, $p<0·001$; Pearson correlation coefficient). The distribution of subjects by AER categories among the three groups of limited joint mobility was statistically different ($p<0·002$, χ^2 test, table 2). Forty six percent of subjects with stage 2 limited joint mobility had AER values above 30 μg/min compared with 23% of subjects with stage 1 and 15% of subjects without limited joint mobility.

Using actual values, the joint classification also correlated significantly with the grade of

Table 1 Demographic data of subjects with various stages of limited joint mobility

Stage of limited joint mobility	*No (%)*	*Mean (SEM) age at last visit (years)*	*Mean (SEM) duration of diabetes (years)*	*Sex (M/F)*	*Smoking (Yes/No)*	*Mean (SEM) blood pressure (mm Hg)*		*Mean (SEM) HbA$_1$ (%)*	*Mean (SEM) cholesterol (mmol/l)*
						Systolic	*Diastolic*		
0	265 (74)	19·5 (0·2)	10·5 (0·2)	123/142	201/64	114·4 (0·7)	71·5 (0·5)	11·40 (0·09)	4·6 (0·05)
1	66 (19)	21·0 (0·5)	14·0 (0·6)*	40/26	47/19	116·3 (1·3)	70·2 (1·3)	11·73 (0·19)	4·7 (0·09)
2	26 (7)	19·5 (0·8)	14·0 (0·8)*	15/11	19/7	118·9 (2·5)	76·7 (1·6)*	12·47 (0·82)*	5·1 (0·23)*
p Value		>0·05†	0·001†	>0·05‡	>0·05‡	>0·05†	0·005†	0·0014†	0·024†

*Significantly different when compared with value for no limited joint mobility (stage 0), using Dunnett's multiple *t* test.
†Analysis of variance.
‡χ^2 test.

*Table 2 Number (%) of subjects as classified by limited joint mobility and AER**

AER (μg/min)	*Limited joint mobility*		
	Stage 0	*Stage 1*	*Stage 2*
<7·6	158 (60)	35 (53)	8 (31)
7·6–30	67 (25)	16 (24)	6 (23)
>30	40 (15)	15 (23)	12 (46)
Total	265 (100)	66 (100)	26 (100)

*χ^2 test=0·002.

Table 3 Number (%) of subjects as classified by limited joint mobility and grade of retinopathy

Eye grades	*Limited joint mobility*		
	Stage 0	*Stage 1*	*Stage 2*
1	106 (40)	14 (21)	2 (8)
2	98 (37)	17 (26)	9 (34)
3–6	61 (23)	35 (53)	15 (58)
Total	265 (100)	66 (100)	26 (100)

*χ^2 test=0·001.

retinopathy (r=0·36, p<0·001; Pearson correlation coefficient). The distribution of subjects by grade of retinopathy and limited joint mobility was also significantly different (p<0·001, χ^2 test, table 3). Subjects with limited joint mobility had more advanced diabetic retinopathy as compared with subjects without limited joint mobility.

Multivariate logistic regression was used to assess the relative importance of gender, duration of diabetes, blood pressure, mean HbA_1 concentrations, smoking status, and cholesterol concentrations on AER and retinal grades. When age, sex, duration of diabetes, smoking, cholesterol, and blood pressure were controlled using the logistic regression model, limited joint mobility remained significantly associated with diabetic retinopathy and AER values (as described in methods). However, when HbA_1 was included in this model, limited joint mobility remained significantly associated only with diabetic retinopathy.

Using logistic regression with limited joint mobility as a response variable, the only factors having a significant effect were duration of diabetes and mean HbA_1 values.

Discussion

Twenty six percent of the 357 young subjects with insulin dependent diabetes in this study demonstrated limited joint mobility. The presence of limited joint mobility was significantly associated with the duration of diabetes, with longitudinal HbA_1 and cholesterol concentrations, and with diastolic blood pressure. The latter three factors were primarily associated with stage 2 joint contractures (table 1). Joint contractures of the fingers were also significantly associated with a greater likelihood of having increased AER and retinal changes. However, when longitudinal HbA_1 concentrations were considered in the logistic regression model, only diabetic retinal changes remained significantly associated with limited joint mobility.

The relationship between limited joint mobility, diabetic renal and retinal complications, and glucose control has previously been confusing. The initial study noting the association of limited joint mobility with microvascular disease did not attempt to differentiate between renal and retinal damage.[8] It is now known that there is a relationship between longitudinal glucose control, as monitored by longitudinal HbA_1 concentrations, and both the renal and the retinal complications of diabetes.[4] Increased glycosylation of connective tissue has been shown in biopsy specimens of skin taken from diabetic subjects with limited joint mobility. However, several studies have not shown a relationship between HbA_1 and limited joint mobility. The most likely reason for this relates to previous studies using a single HbA_1 value, reflecting glucose control for only a short period. This single value may not be representative of the accumulative effect of glucose control over the many years of having diabetes. In the present study, when longitudinal HbA_1 concentrations from a mean period of 7·6 years were studied, the limited joint mobility clearly related to the HbA_1.

Another reason for the variability in reports of the relationship of limited joint mobility and diabetic renal and retinal complications and glucose control relates to inadequate statistical methods used in most previous papers. Most previous studies have not evaluated the effect of limited joint mobility on the renal and retinal complications when controlled by longitudinal HbA_1 concentrations using a multivariate statistical model. When logistic regression analysis was used in the present study, limited joint mobility had no statistically significant influence on diabetic renal disease, although a significant effect on retinal disease remained. In the only other study of limited joint mobility in which logistic regression models were used (in adults with non-insulin dependent diabetes), limited joint mobility was also found to be significantly associated with retinopathy, but not with the AER.[10]

The main association of limited joint mobility and HbA_1 concentrations was for subjects who had two or more joints involved (table 1). Studies in which different grades of involvement were not considered in the statistical analysis might have missed this association. It is our current hypothesis that when only the interphalangeal joints of the little finger are involved, a genetic aetiology may be predominant. However, when other joints are also involved, longitudinal poor glucose control is likely to be a major factor. In support of this hypothesis is the frequent finding of limited joint mobility of the interphalangeal joints of the little finger in first degree relatives of children with insulin dependent diabetes.[9] However, we have never seen involvement of other joints in non-diabetic first degree relatives.

The mechanism by which limited joint mobility continues to influence retinal changes, even when the effect of longitudinal HbA_1 concentrations are taken into account is unknown. It has been suggested that the initial lesion in the retina relates to loss of endothelial connective tissue support cells. Possibly, similar changes in connective tissue might also occur in the skin and joint capsules. The pathophysiology of diabetic retinopathy is also related to factors other than just longitudinal glucose control, such as the duration of diabetes.[4] Duration of diabetes was also found to be related to the presence of limited joint mobility in the present study. Further studies are clearly needed to identify other factors influencing the development of diabetic retinal disease.

Our data suggest an association of joint contractures with the eye complications of diabetes. HbA_1 was an important factor influencing joint contractures. The association of joint contractures with eye (but not kidney) changes remained when HbA_1 concentrations (and other variables) were included in the multivariate model.

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Failure to prevent nicotine addiction in young people with diabetes

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Abstract

The habit of smoking is usually acquired at a young age and it is particularly undesirable in individuals with diabetes. A study was carried out to assess objectively the prevalence of smoking in young patients with diabetes and whether younger age at onset of diabetes (implying exposure to health education) reduced the incidence of smoking. Ninety nine young adults with diabetes attending the routine clinic were studied using a structured interview and assay of a urinary nicotine metabolite (cotinine). Forty eight percent of the cohort were smoking (raised urinary cotinine), although only 31% admitted to smoking. Thirty eight percent of the patients with childhood onset diabetes, 56% of the adolescent onset, and 47% of the young adult onset patients were smoking. Smoking was not related to glycaemic control or body mass index. In conclusion, smoking is common in young patients with diabetes and is often denied. Conventional health education does not appear to prevent children and adolescents with diabetes from starting to smoke. Antismoking policies and health education must therefore be reinforced and improved.

People with diabetes have a greatly increased prevalence of coronary artery, cerebral, and peripheral vascular disease.[1] Cigarette smoking is another major risk factor for the development of atheroma and may interact with diabetes to magnify its atherogenic effect.[2] Smoking has also been implicated in the development and progression of diabetic microvascular disease (nephropathy and retinopathy).[3] In a recent consensus statement, the American Diabetes Association has stressed the importance of people with diabetes not smoking and recommends aggressive attempts to deter people from acquiring the habit and to persuade smokers to stop.[4] A smoking habit is usually established in adolescence and nicotine addiction is so powerful that most smokers are unable to stop, despite wishing to do so.[5] It is obviously a very serious event if a young person with diabetes becomes addicted to nicotine. In order to assess the extent of nicotine addiction we have surveyed the smoking habits of young people with insulin dependent diabetes attending our young adult diabetic clinic. In addition we wished to ascertain whether the antismoking counselling and health education given to patients who developed diabetes in childhood and adolescence had been successful in preventing smoking. The validity of the smoking history was assessed using urinary cotinine (a nicotine metabolite) measurement.

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Patients and methods

Ninety nine consecutive insulin dependent diabetic patients attending the young adult clinic at Walton Hospital Diabetes Centre, Liverpool were studied (53 male). The mean (SD) age was 21·5 (3·9) years (range 15–31 years). The mean (SD) duration of diabetes was 7·3 (5·2) years (range 0·5–24 years). All had normal renal function (serum creatinine concentration <100 μmol/l). Twenty four patients had developed diabetes as children (0–10 years of age), 43 as adolescents (11–15 years of age), and 32 as young adults (>15 years of age). The patients who had developed diabetes in childhood or early adolescence were usually transferred from the local paediatric diabetic clinic at the age of 16 years.

The young adult clinic had been established by one of the authors (IAM) six years previously. During this time all patients had received regular antismoking counselling from the same doctor stressing the health effects of smoking and the added risk of retinopathy and nephropathy. At the paediatric diabetic clinic older children and their families are warned of the adverse health effects of smoking.

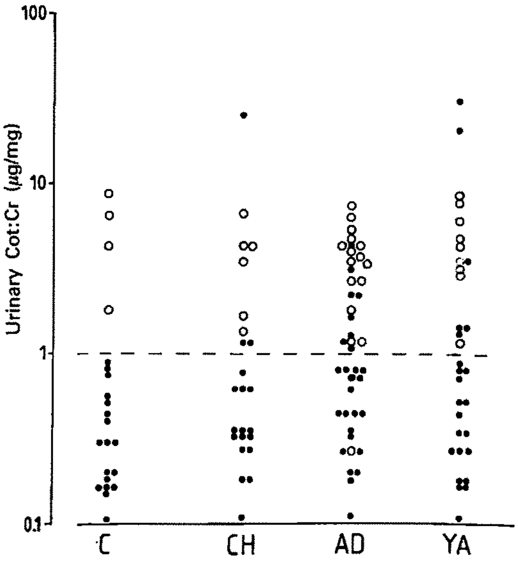
A questionnaire on smoking was completed by each patient with the help of a diabetes specialist nurse (MEW), with questions relating to current or past smoking habit, age of starting smoking, details of family smoking habits, knowledge of health effects of smoking, and attitudes to smoking. Whole blood glycated haemoglobin (HbA_1, non-diabetic range <8%) and body mass index (BMI) were also measured. An aliquot of the urine sample that had been tested for glucose and protein at that visit was assayed for cotinine with a polarisation fluroimmunoassay using commercial reagents (Perkin-Elmer). The urinary cotinine:creatinine ratio (Cot:Cr) in μg/mg was calculated in order to allow for variations in urine volume. The patients were not told in advance of the questionnaire that their urine sample was to be tested for cotinine. No patient claimed to use nicotine chewing gum or other nicotine containing products. Control subjects for the cotinine assays were 22 non-diabetic hospital staff who were aware that their smoking history was being validated by urinary cotinine measurements. Eighteen of these controls denied smoking and four were regular smokers.

Standard parametric and non-parametric statistical methods were used as appropriate.

Results

The distribution of urinary Cot:Cr ratios of the patients with diabetes and the non-diabetic controls who claimed to smoke and those who denied doing so is shown in the figure. The patients with diabetes are displayed as three groups (childhood onset diabetes, 0–10 years old; adolescent onset, 11–15 years old, young adult onset, >15 years old). In the control subjects there was a clear separation in the Cot:Cr ratios between those who admitted to smoking and those who denied doing so. The non-smoking range of Cot:Cr ratios in the controls was 0·1–0·9 µg/mg (median 0·3). Cot:Cr ratios above this range (≥1 µg/mg) were therefore taken to indicate active smoking in the preceding 24 hours. Of the 99 patients with diabetes, 31 (14 female) admitted current smoking and 14 said they were ex-smokers. However from the figure it can be seen that 17 of the 68 who claimed not to smoke had Cot:Cr ratios greater than 1 µg/mg suggesting active smoking. Therefore, including these 17 patients, 48 (48·5%) of the study group were smoking (25 female). This objective marker of smoking demonstrated that the habit was common in all three groups of diabetic patients and there was no significant differences between them (38% childhood onset, 56% adolescent onset, 47% young adult onset). There was no significant difference in the concentration of cotinine in the urine of the three groups of patients.

The median age at starting smoking for those who admitted the habit (65% of smokers) was 16 years (range 10–20 years). Cot:Cr ratios were not related to glycaemic control (smokers mean (SD) HbA_1 was 11·8 (2·9), non-smokers 10·8 (2·6); this was not significant). BMI and smoking were not related (smokers mean (SD) BMI was 22·9 (2·9); non-smokers 23·8 (2·8); this was not significant). The 48 diabetic smokers were all aware that smoking had deleterious effects on health and 86% of them were aware that smoking could make diabetic complications worse. Smoking was common in the families of the patients with diabetes who were smokers: 38 of the 48 smokers lived with one or more family members who smoked. However 30 of the 51 non-smokers also had a household family member who smoked. The great majority (90%) of admitted smokers wished to stop (generally because of health worries) and many had tried unsuccessfully to do so.



Results of urinary Cot:Cr in µg/mg. Groups according to age at onset of diabetes: C=control; CH=childhood (0–10 years); AD=adolescent (11–15 years); YA=young adult (>15 years). Open circles are subjects admitting to smoking; closed circles are subjects who denied smoking. Note vertical log scale. Broken line represents the division between active smoking and non-smoking levels.

Discussion

Urinary cotinine is the best measure of smoking activity, reflecting the number of cigarettes smoked in the previous 24 hours in people with normal renal function.[6] The importance of using an objective measure of active smoking in people with diabetes is well established.[7–9] This study in young patients with insulin dependent diabetes again illustrates that answers to smoking questionnaires must be viewed with caution. Thirty one percent of the patients in this study admitted to smoking but the urinary cotinine assay suggested that up to 48% were in fact smoking. We have no objective data on the smoking habits of the local non-diabetic young adult population, although questionnaire surveys indicate that 25–35% of young adults admit to smoking.[5] It is possible that many of our young patients denied their smoking habit because they did not want to disappoint the nurse specialist or the doctor in the clinic. A similar phenomenon occurs when patients falsify the results of home blood glucose and urine glucose measurements in order to please their medical attendants.[10]

It is clear from our results that the diagnosis of diabetes in childhood and the antismoking advice at the paediatric and young adult diabetic clinics does not have a significant influence on the subsequent acquisition of a smoking habit. Also the diagnosis of diabetes and antismoking advice in the young adult smoker appears to have little effect on nicotine addiction already present. We have previously suggested that people with diabetes may have particular difficulty in stopping smoking, perhaps because of the social and dietary constraints that diabetes already imposes.[7 9] The reduction of nicotine addiction in our young patients is a major challenge because this habit undoubtedly increases the already substantial risk of developing macrovascular disease and may exacerbate microvascular disease. Physicians caring for young people with diabetes should consider using objective markers of smoking such as urinary cotinine measurements, and must devise more effective methods of preventing nicotine addiction and assisting smokers to stop.

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Do doctors recognise eating disorders in children?

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Abstract

The aim of this study was to determine whether doctors recognise eating disorders in children, in particular anorexia nervosa. A group of paediatricians, general practitioners, and school medical officers was approached to participate in the study. Each was sent a questionnaire including two case vignettes of children with anorexia nervosa and questions about diagnosis and management. The response rate was 64·5%. Of 97 different diagnoses suggested, only one quarter were psychiatric or psychological. One third of the paediatricians mentioned anorexia nervosa within their differential diagnosis in both cases compared with 2% of primary care physicians. These results suggest that doctors' awareness of childhood onset eating disorders remains limited. A delay in appropriate treatment has potentially adverse consequences for prognosis.

Families of children with an eating disorder may spend many months consulting a variety of health professionals before being referred to child psychiatry. We found an average period of 7·4 months between parents first seeking advice about eating problems and referral to our clinic.[1] Often this delay appears due to the doctors consulted failing to recognise the eating disorder. We believe this frequently impedes our ability to provide effective treatment as the eating disorder becomes more entrenched and parents focus on medical instead of emotional/behavioural issues. In older patients with an eating disorder, a shorter history of illness before treatment has been found to be a predictor of good outcome.[2–5] By implication, a delay between onset and treatment may be unfavourable in terms of prognosis. We therefore addressed the question: Do doctors consider a diagnosis of eating disorder in children? This is a prerequisite to early intervention.

The epidemiological literature suggests that it is difficult to identify eating disorders at a primary care level as prevalence rates are low, especially for children.[6] Nevertheless, we have seen an increase in the number of children referred for treatment of an eating disorder over the past decade; most receive a diagnosis of anorexia nervosa but some are diagnosed as having 'food avoidance emotional disorder'[7] or more idiosyncratic forms of food refusal[8] or selective eating patterns. As anorexia nervosa is the most commonly encountered formally diagnosable eating disorder in the population we serve (8–14 years), this was the focus of the study.

The aims of the study were to: (1) Discover to what extent 'anorexia nervosa' in particular and 'eating disorder' in general are considered possible diagnoses in children. (2) Discover how likely doctors are to consider a psychological explanation for presenting eating difficulties and to ascertain what effect this has on management. (3) Identify the existence of any common patterns of management and referral of such children. (4) Determine whether there appear to be any differences between primary care doctors and paediatricians in the above respects.

Methods

All paediatricians and school doctors and a random selection of one general practitioner from each of a number of group practices listed within a defined geographical region were approached. Of these 140 doctors, 56 (40%) were paediatricians, 38 (27%) school medical officers, and 46 (33%) general practitioners. All were sent a four page questionnaire and a signed covering letter omitting detail of title, post, or profession.

The questionnaire included two short case vignettes based on children seen at our eating disorders clinic, describing *common presenting features* of children with anorexia nervosa. The first concerned an 11 year old girl experiencing abdominal pains, nausea, and occasional vomiting for the previous three months after a urinary tract infection treated with antibiotics. Because of these symptoms she had not felt like eating and agreed that she had lost weight. Previously of average weight and height for her age, she had lost 10 kg. Examination reveals only that she is thin and complaining of generalised tenderness in the abdomen.

The second case concerned an 11 year old boy about whom there had been concern regarding weight loss, although he considered himself well. Also of average weight and height for his age previously, he had lost 10 kg over the past three months. He had become moody, withdrawn, and fussy about meals, eating a restricted range of foods very slowly. On examination he is very thin but no other significant abnormality can be found.

Doctors were asked to suggest a *provisional* diagnosis and two differential diagnoses for each of the two cases. Using a given scale, they then rated a series of management options in terms of how likely they would be to implement them initially. Finally, the doctors indicated further steps if the results of blood and urine tests undertaken proved normal.

Statistical analysis was by χ^2 which was

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corrected for continuity using Yates's procedure. Where this differed from the uncorrected value, Fisher's exact test was carried out.

Results

DIAGNOSIS

Two letters were returned unopened and 89 of the 138 potential responders (65%) replied. Of these, 33 (60%) of the paediatricians returned completed questionnaires compared with 46 (55%) of general practitioners and school doctors (not significant: χ^2=0·13, df=1, p>0·05). Data from one paediatrician who had been practising as a geneticist were excluded. As many school doctors also worked as general practitioners, data from these primary care physicians were combined.

Some doctors gave more than one provisional and two differential diagnoses and some gave less. In all, 97 different diagnoses were suggested, approximately a quarter of which (n=25) were psychiatric/psychological. Diagnoses relating to gastrointestinal (n=24) and renal (n=15) disorders were other common groups. The remaining 33 diagnoses included a range of disorders.

In addition to anorexia nervosa the psychiatric diagnoses related to eating included food refusal, disorder of eating behaviour, psychogenic anorexia, pyschiatric disturbance with anorexia, and food fetishism, although each of these was mentioned by only one physician. Significantly more paediatricians than primary care physicians suggested anorexia nervosa in each case, yet only 31% (n=10) of paediatricians and 2% (n=1) of primary care physicians mentioned it in *both* cases. Renal disease and gastrointestinal diagnoses were suggested far more frequently than eating related disturbances in case 1 by both groups of doctors (see table 1).

No significant sex differences were found. Of the 54 male respondents and 25 female respondents, 48% made at least one diagnosis of an eating problem; 44% of each sex specified anorexia nervosa.

MANAGEMENT

In both cases the majority indicated that the initial step in management would be to arrange blood and urine investigations, then see the child again (table 2). Early referral to a paediatrician (or paediatric colleague) was also considered by over half of both groups of doctors. In case 1, referral to a mental health specialist was specified by 16% of paediatricians and 9% of the primary care physicians after having seen the child only once; the figures for case 2 were 50% and 30% respectively (see table 2).

After normal blood and urine test results primary care physicians were significantly more likely than paediatricians to consider referral to a paediatrician or paediatric colleague (χ^2=7·811, p<0·01), but this pattern was reversed for referral to other named specialists (see table 2). Referral to a mental health specialist was mentioned by 38% of paediatricians and 26% of primary care physicians in case 1 (χ^2=0·680, p>0·05) compared with 72% of paediatricians and 43% of primary care physicians in case 2 (χ^2=5·057, p<0·05).

Discussion

It is, of course, unlikely that a doctor would make a diagnosis on the basis of such limited information as that provided in the case vignettes. However, doctors were not asked for a definitive diagnosis and the aim was to gain an impression of whether an eating disorder might be suspected in children presenting with features of anorexia nervosa accompanied by significant weight loss.

Table 1 Diagnoses: number (%) of doctors making different types of diagnoses

	Psychiatric			*Renal*	*Gastrointestinal*	*Other*
	Anorexia nervosa	*Eating related disorder*	*Other*			
Case 1:						
Paediatricians	13 (41)*	2 (6)	7 (22)	27 (84)	18 (56)	17 (53)‡
Primary care physicians	6 (13)*	1 (3)	15 (33)	41 (90)	20 (43)	32 (70)‡
Case 2:						
Paediatricians	18 (56)†	2 (6)	11 (34)	3 (11)	8 (25)	18 (56)
Primary care physicians	9 (20)†	1 (3)	30 (65)	11 (24)	14 (30)	31 (67)

*χ^2=6·367, p<0·05; †χ^2=9·659, p<0·01; ‡χ^2=7·850, p<0·01.
Total paediatricians, n=32, and primary care physicians, n=46.

Table 2 Management: number (%) of doctors making different management decisions

	Initially					*After normal test results*			
	Blood/urine tests	*Refer to paediatrician*	*Refer to other specialist*			*Refer to paediatrician*	*Refer to other specialist*		
			Unspecified	*Mental health*	*Other*		*Unspecified*	*Mental health*	*Other*
Case 1:									
Paediatricians	27 (84)	19 (59)	8 (25)	5 (16)	4 (13)	19 (59)*	4 (13)	12 (38)	6 (19)
Primary care physicians	37 (80)	33 (72)	12 (26)	4 (9)	9 (20)	41 (89)*	10 (22)	12 (26)	5 (11)
Case 2:									
Paediatricians	26 (81)	17 (53)	7 (22)	16 (50)	0	19 (59)	2 (6)	23 (72)†	0
Primary care physicians	33 (72)	24 (52)	8 (17)	14 (30)	0	37 (80)	10 (22)	20 (43)†	0

*χ^2=7·811, p<0·01; †χ^2=5·057, p<0·05.
Total paediatricians, n=32, and primary care physicians, n=46.

Results suggest that, in general, paediatricians are more likely than primary care physicians to consider a diagnosis of eating disorder in children presenting with eating problems and weight loss. Only one third of paediatricians (31%) questioned the possibility of anorexia nervosa in both cases, compared with a mere 2% of primary care physicians. In the case of presentation after a urinary tract infection, the number of doctors suggesting anorexia nervosa was especially low. This presentation may appear quite atypical and it is acknowledged that urinary tract disease is more common than eating disorder. However, it is not unusual for eating disorders to present with a wide range of physical symptoms masking the underlying psychopathology and limiting the physician's ability to identify eating disorders in the early stages.[9]

It has been suggested that general practitioners may have a low index of suspicion for eating disorders and are poor at recognising eating disorders or making a link between psychological problems and eating difficulties, impeding effective treatment.[10-11] The results of this study appear to support these general findings.

In terms of management, basic blood and urine screening was the most usual preferred step. About half of both groups of doctors indicated that they would see the child at least three times before referring them on. This did not appear to be related to diagnosis, suggesting that where an eating disorder might be suspected, early referral to mental health colleagues may not occur. The tendency for general practitioners not to refer their patients with eating disorders has been reported elsewhere.[12]

In this study, after normal test results primary care physicians showed a significantly greater tendency to refer to paediatricians than the group of paediatricians did to refer to paediatric colleagues. In turn, paediatricians showed a non-significantly greater tendency than the primary care physicians to refer to another specialist.

One of the further aims of the study was to determine the extent to which a psychological basis was considered. It can be extrapolated from the numbers of doctors making a psychiatric/psychological diagnosis. Paediatricians did so at slightly higher rates than primary care physicians, which is presumably related to their higher tendency to refer to mental health specialists.

In conclusion, these findings appear to show that physicians' awareness of childhood onset eating disorders remains rather limited, particularly that of primary care physicians. This is of some concern given that children are most likely to present to these doctors in the early stages of their eating disorder. Although more inclined to consider a diagnosis of anorexia nervosa, the majority of paediatricians made no mention of any eating disorder in at least one of the two cases. We conclude, therefore, that the diagnosis of eating disorder may often be missed in young children, resulting in a delay in the initiation of appropriate treatment and a possible poor effect on prognosis.

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Trial of intensive compared with weekly speech therapy in preschool children

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Abstract

Forty two preschool children referred to a speech therapy department were randomly allocated to receive intensive individual speech therapy or the more traditional once weekly approach. Boys and minority ethnic groups were referred most frequently. Speech therapy improved expression more than comprehension, as measured on Reynell scales. The mean improvements were 0·5 SDs (95% confidence intervals (CI) 0·3 to 0·7) and 0·3 (95% CI 0·1 to 0·5) respectively. There was a greater improvement in children receiving intensive compared with weekly therapy in the expression scores (0·8 SDs (95% CI 0·5 to 1·1) *v* 0·2 SDs (95% CI −0·1 to 0·5)). White and non-white children had similar improvements in comprehension scores but white children had greater improvement in expression scores (1·1 SDs *v* 0·3 SDs). This difference was seen in both therapy groups. Randomised trials are useful in the evaluation of speech therapy in children.

In order to maximise the effectiveness of services, different patterns of speech therapy for children are being developed,[1] but their evaluation has been limited. The most common pattern to emerge is intensive group therapy. While an assessment of outcome of this approach has not been published, Richardson (P Richardson, unpublished report to Warrington Health Authority, 1987) and Onslow[2] have suggested that this approach leads to increased attendances, increased throughput, and greater acceptability. However, it is not known whether it is the group environment or the intensive nature of the therapy that is the most important factor. In addition, speech therapists are increasingly concentrating on preschool children, because early intervention may modify the cause and impact of childhood speech and language disorders (S Roulstone, P Ison, unpublished report to Bristol and Western Health Authority, 1987).[3]

The speech therapy department in Wandsworth health district was receiving increased referrals without an increase in resources. This resulted in delays of six months for initial appointments in community clinics and some day nursery children not completing their course of therapy before entering school. A structured review of the services is being undertaken to assess the most cost effective way to provide speech therapy services to the local community. As part of this process, a first step was to compare the benefits of intensive individual speech therapy with the more traditional once weekly approach. This paper presents the results of a randomised trial assessing the efficacy of two patterns of treatment as well as their acceptability.

Patients and methods

PATIENTS

Children attending 15 day nurseries or special play groups, and three nursery classes attached to mainstream schools in the health district of Wandsworth (south west London) who were referred to the speech therapy department, were randomised to receive either an intensive course or a weekly session. In order to minimise bias within one establishment, the randomisation using random number tables was by place of referral rather than by person. To be eligible for the study children had to be aged between 2 and 5 years with no major physical or mental handicap. All children had to demonstrate limited communication in the nursery as reported by staff and fall into diagnostic categories of (a) developmental language delay, (b) a language delay which may have no identifiable cause, or (c) be associated with bilingualism or severe deprivation.[4] Because of the possible effects of attendance at a preschool playgroup on accelerated language growth, it is local policy that children are only referred to the speech therapy department after one term in a school or three months in a day nursery. In addition, children had to be at least one standard deviation below the mean for his/her age on the Reynell development scales in comprehension, expression or both.[5] Children had to attend at least 80% of the sessions to be eligible for the study.

TREATMENT

Treatment was carried out by three therapists who undertook both patterns of therapy. The weekly course was carried out by a speech therapist visiting the nursery one day a week for 40 minutes per child, over a six month period, with a possible maximum of 24 attendances per child. Intensive therapy consisted of a 40 minute session, four days per week for three weeks, in each three months of a six month period, giving a maximum of 24 attendances per child. All therapy programmes by the three therapists were devised for the individual child. The overall approach was that of language development through play, focusing on the areas of individual need for development of form, use, and content of language. This was followed by structured work according to the child's need for particular aspects of language. In addition, individual programmes addressed to associated and/or underlying problems of attention, perception, and communication.

MEASUREMENTS

Outcome of the trial was assessed by changes in the Reynell scales over a six month period.[5] These were measured as SD from the value expected for a child of that age. To allow for minor differences in starting scores, changes over the six months were calculated by deducting the second from the first score. Differences in the means between the two groups were analysed by Student's two tailed *t* tests. Because it was not practical to balance or randomise all the important confounding factors, these were taken into account in the final analysis.

Recruitment of large numbers of patients within the time available was not possible. It was anticipated that 20 patients would be recruited into each group which would give a 90% chance of demonstrating a difference of approximately 0·5 Reynell SDs, which is considered clinically relevant.

Questionnaires on the acceptability of the intensive therapy were designed for the study. They were completed by the officers in charge or heads of the day nurseries and nursery classes. Questions included the convenience of the new working pattern, quality of service provided, and the effects of speech therapy on children's participation in everyday events. The scales and questions were administered by an independent speech therapist who was not involved in treatment.

Results

Forty two children were recruited; two children from the weekly group and one child from the intensive group did not complete the 80% attendance required and were excluded from the analysis.

The characteristics of the children are shown in table 1. Over the six months both groups showed an improvement in comprehension score (p=0·07 for intensive group, p=0·02 for weekly group) but the difference between the two groups was not significant. In the expression scores both groups showed an improvement (p=<0·01 for intensive group and p=0·18 for weekly groups) but the intensive therapy showed significantly greater improvement (an additional half SD).

Table 1 Characteristics of children in each treatment group. Results are mean or number (95% CI)

	Intensive (n=18)	*Weekly (n=21)*	*p Value**
Age (years)	3·4 (3·1 to 3·6)	3·5 (3·2 to 3·7)	
Sex M/F	12/6	15/6	
Ethnic group:			
White	7	4	
Afro-Caribbean	9	16	
Other	2	1	
Therapists:			
A	7	13	
B	8	5	
C	3	3	
Reynell developmental language scales:†			
Comprehension score			
At start	−1·4 (−1·7 to −1·1)	−1·5 (−1·8 to −1·2)	
At six months	−1·1 (−1·5 to −0·7)	−1·2 (−1·7 to −0·9)	0·56
Improvement	0·3 (0 to 0·6)	0·3 (−0·1 to 0·5)	0·86
Expression score			
At start	−1·1 (−1·5 to −0·7)	−1·3 (−1·7 to −0·9)	
At six months	−0·5 (−0·7 to −0·3)	−1·1 (−1·5 to −0·7)	0·02
Improvement	0·8 (0·5 to 1·1)	0·2 (−0·1 to 0·5)	0·05

*Student's two tailed *t* test.
†Measured as number of SDs from the expected Reynell developmental score standardised for age.

There were no significant differences in the effectiveness of the three therapists.

Overall 69% of the children were boys. There were no significant differences between the sexes in comprehension and expression scores at the beginning of the study. There was no sex difference in the change in comprehension score (mean improvement 0·3 SD), but girls tended to have a greater improvement in expression scores (mean improvement 0·6 SD *v* 0·3 SD, p=0·2).

The ethnic analysis showed 72% of children were not white. There was little difference between the comprehension scores of white and non-white children (−1·4 SD, −1·5 SD) and expression scores (−1·6 SD, −1·1 SD) at entry into the study. White and non-white children had similar improvement in comprehension scores (0·1 SD, 0·4 SD, p=0·28) but white children had greater improvement in expression scores (1·1 SD, 0·3 SD, p=<0·01). In order to assess the independent contribution of type of speech therapy and ethnicity to the change in expression score the analysis was repeated, controlling for ethnicity. Table 2 shows that in white children the mean improvement in the intensive therapy group was 1·2 SD (95% confidence intervals (CI) 0·8 to 1·6) and 0·8 SD (95% CI 0·7 to 0·9) in the weekly group. In non-white children the mean improvement in the intensive group was 0·5 SD (95% CI 0·2 to 0·8) and in the weekly group 0·1 SD (95% CI −0·2 to 0·4). The difference between type of therapies in white and other children was the same (0·4 SD) which is 0·2 SD less than the overall difference. This is due to a higher proportion of low scoring non-white children in the weekly group. When multiple regression analysis was undertaken with the change in expression score as the dependent variable and ethnic group and type of therapy as the independent variables, 35% of the variance in expression score could be explained by these two variables. The addition of sex into the equation did not significantly increase the amount of variance explained.

Of the six establishments that had received intensive therapy, three considered it to be an improvement on the weekly sessions, two did not, and one was unsure. The advantages of intensive therapy were that the child quickly built up a relationship with the therapist which was maintained; it did not need to be re-established every week. The same was perceived

Table 2 Changes in the Reynell expression scores in the two treatment groups, controlling for ethnic origin

Ethnic origin	*Mean change in expression score*		
	Intensive	*Weekly*	*Difference*
White	+1·2 (n=7)	+0·8 (n=4)	0·4
Other	+0·5 (n=11)	+0·1 (n=17)	0·4

as applicable to the staff. The disadvantages were the difficulty in fitting into the other care programmes and the lack to follow up after the period had finished. (Detailed comments are available on request.)

Discussion

There is immense variation in the rates children acquire language.[6] The reasons range from normal variation to severe underlying pathology, such as hearing loss. After excluding an 'organic cause' for a child's language difficulty which is giving concern to parents, nursery teachers, or doctors, the assessment and treatment should then be by a qualified speech therapist.[7] Little evaluation of the effectiveness of different types of therapy has been attempted. This study is one of the first to publish the results of speech therapy and suggests that, in an inner city district, minority ethnic groups are more likely to be referred for treatment. The findings that boys are referred more frequently than girls reflect the general patterns in the UK. Speech therapy appears to improve expression more than comprehension and intensive therapy is likely to be better than weekly therapy. Ethnic minority groups will need more help to improve their expression scores. Whether this means more of the same therapy for ethnic minorities or a different type of therapy is unclear. It may be that therapy programmes designed along the lines of language development in English give white children an advantage when assessed on the Reynell scales.

This study was designed to assess two patterns of speech therapy; it did not have a control group so we do not know what effects a preschool environment alone has on speech and language development. The delay in referral, however, should have minimised any beneficial effects of a preschool placement on the trial results. Each type of placement will have a different approach to language based activities but the randomisation should have ensured that these effects were equally distributed in both treatment groups. Randomised controlled trials of new treatment usually have a control or placebo study, but incorporating this design into an established pattern of care, where practitioners already have opinions on treatment, has proved difficult in many branches of medicine.[8] Trials have been considered inappropriate for evaluating speech therapy[9] but in the 'new' NHS, assessment of services will be required as therapists will be increasingly accountable for both their client selection and the efficacy of their procedures.[10]

Measurement of the outcome of a clinical trial where the treatment is a service are notoriously difficult.[11] In this study, a numerical score was obtained for two aspects of language based on a recognised scaling system. In addition, the perception of the supervisors of these children was obtained. Scales are only a surrogate for the clinical outcome you are hoping to achieve. In order to have confidence in their application, good repeatability and validity needs to have been demonstrated. It has been accepted that the Reynell scales are useful in describing the level of language development of an individual.[7] We have used the change in Reynell scale scores as an indicator of the difference in the language characteristics of a child. This assumes that the therapy did not merely train the children to perform well on the scales. Additional criticisms of this approach to assessment are twofold: first, that the improvement may be only in the context of the treatment environment and does not represent a child's capabilities in the normal environment; and secondly, that the treatment makes no change in an absolute sense to the patient but merely enables the child to reach his/her level of development more quickly. However, much rehabilitative medicine is based on this latter principle and seen as a legitimate aim, particularly in speech therapy for children under 5 years old where its aim is to bring language to the normal level for age, before school entry.

With these provisos, the next step in our review of childhood speech therapy services would appear to be randomised controlled trial of intensive individual and intensive group therapy with a control study. Further research into the differing requirements of ethnic minority groups will be part of this evaluation.

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Home parenteral nutrition in chronic intestinal failure

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Abstract

In children with severe failure of intestinal function, intravenous nutrition is at present the only treatment able to maintain adequate nutrition for prolonged periods of time. Over the last five years we have discharged 10 patients home on parenteral nutrition for a total of 25 patient years and here the outcome of these children is presented. Of the 10 patients, one has discontinued home parenteral nutrition (HPN), seven patients remain well, one patient has recently moved to the USA, and one patient has died after major abdominal surgery. All children had either normal or an accelerated rate of growth on HPN and developmentally all have progressed well. All the children over 5 years attend normal schools. The major complication of treatment was line sepsis with an overall rate of one episode in 476 days and a total of nine central lines (five patients) have required replacement giving an average line life of 680 days. For those children unfortunate enough to suffer from severe intestinal failure, HPN is preferable to prolonged hospital treatment and offers the chance of a good quality of life with prolonged survival.

In early childhood inadequate nutrition readily results in stunting of growth and the development of multiple nutritional deficiencies. Where nutritional requirements cannot be met by the enteral route as a consequence of severe gastrointestinal disease and intestinal failure, parenteral nutrition offers a method for maintaining normal growth and development.[1–5] As a result of developments both in the formulation of parenteral feeding regimens and in the insertion and nursing care of central venous catheters it is now possible for this to be carried out safely for many years.[6]

However prolonged hospital admission has a detrimental effect on the development of young children and is very disruptive to family life. Home parenteral nutrition (HPN) has been available in selected units within the UK for over 10 years in adult patients,[7–9] but it is only more recently with improvements in parenteral nutrition care that HPN has become available for younger patients. Provisional studies already suggest that the growth and intellectual development of children fed at home parenterally is accelerated after discharge from hospital.[10]

In this paper we describe the selection, organisation, and outcome of 10 children whom we have treated at home with HPN for a total of over 25 patient years and emphasise those aspects peculiar to the UK.

Patients and methods

PATIENTS

A total of 10 children (five girls, five boys) have been discharged from our unit on HPN over the last five years. Their ages have varied from 10 months to 15 years (mean 4·6 years) and the length of follow up has ranged from 10 months to 4·9 years (mean 2·6 years). This represents over 25 patient years experience of HPN. Two children have been discharged abroad, one to Italy and the other to Malta, and their care is shared. The details of the patients are listed in table 1.

SELECTION CRITERIA CONSIDERED

The suitability of a child for HPN is dependent on both medical and social factors. The severity of the child's underlying intestinal disease will determine whether complete or partial HPN is required, whether they have large fluid, electrolyte, and vitamin requirements, and will thus influence the complexity of the child's treatment at home.

While it may be possible for the most able parents to care for a child with complex medical problems on HPN, some parents will be unable to cope with the technical and emotional demands of their child's treatment. Thus the parents need to be highly motivated, have a stable relationship, have adequate housing, and to be of average or greater intelligence.

VENOUS ACCESS

In all patients Hickman or Broviac Silastic catheters have been aseptically surgically inserted for the intravenous delivery of nutrients. Our preferred site of insertion is in the right or left subclavian vein with the tip of the central venous catheter lying in the right atrium with the catheter tunnelled onto the chest wall. In some children multiple central venous catheter insertions has meant that jugular and femoral veins have also been used.[6] Single lumen

Table 1 Details of patients who have received HPN

Patient No	*Primary disease*	*Age at discharge (years)*	*Length of follow up (years)*
1	Pseudo-obstruction	3·3	4·9
2	Pseudo-obstruction	1·7	4·8
3	Pseudo-obstruction	15·0	3·6
4	Congenital enteropathy	1·3	3·5
5	Short gut	1·3	2·7
6	Short gut	5·5	0·8
7	Congenital enteropathy	0·8	1·8
8	Short gut	6·7	1·7
9	Congenital enteropathy	1·5	0·8
10	Immunodeficiency	7·4	0·8

catheters are used exclusively with their use strictly limited to the delivery of nutrients.

Blockage of a central venous catheter may occur at the tip from the deposition of fibrin or at the hub due to the precipitation of nutrients or salts from the HPN. Urokinase (5000 U in 3 ml) instilled into the catheter for four hours and repeated on successive days up to a maximum of three, will dissolve fibrin, and 70% alcohol will help dissolve any lipid deposited within the catheter. If the catheter is blocked at the hub, debris may be seen or the lumen may not be visible. Removal of the hub and replacement using a Broviac/Hickman repair kit will restore patency to the catheter. When these methods fail the central venous catheter should be replaced.

NUTRIENTS

In all cases the nutrients were compounded by Baxter Healthcare (nine in UK, one in Italy). Four of the children who have significant residual intestinal function received an amino acid (Synthamin, Baxter)/dextrose mixture as a single infusion. The remaining six children with very little residual intestinal function received intravenous fat (Intralipid 20%, KabiVitrum) in addition on two days of the week. In three the Intralipid was formulated in a single bag giving a lipid/amino acid/dextrose mixture, and in three of the older children the lipid was given as a bolus infusion before the infusion of the amino acid/dextrose mixture.

The electrolyte content of the intravenous nutrition was closely matched to the requirements of the child. Trace elements were added to the infusions: copper, zinc, chromium, and manganese (MTE-4, Baxter) along with sodium selenite 0·02 μmol/kg/day (KabiVitrum). In those patients with some residual absorptive function, fat and water soluble vitamins were given as Ketovite tablets and liquid (Paines and Byrne): six tablets and 10 ml per day (double the normal dose). In two children with very little gut absorptive function, vitamins were given intravenously as Solvito (KabiVitrum) and Vitalipid (KabiVitrum). The shelf life of non-lipid containing nutrient bags is three months and for those containing lipid it is only one month.

The intravenous feeds were given at night over 12 hours and in those children who were not on total HPN this was supplemented by oral feeds during the day. When possible the HPN was given over five or six nights per week to allow the parents a night free.

SUPPLY OF NUTRIENTS

For the patients living in the UK we have exclusively used the services of a commercial homecare company (Unicare Medical Services Ltd, Harlow, Essex) to supply and deliver nutrients and disposables to the child's home. The Maltese child received his HPN by air freight from the UK and the nutrients for the Italian child were manufactured locally. The intravenous nutrient solutions were delivered at intervals of two weeks to the child's home along with the ancillary supplies. Space must be available in the family home to store intravenous feeding solutions, consumables, and the items of equipment listed in table 2.

FUNDING

The intravenous nutrient solutions were prescribed by the child's general practitioner on a FP10 form and the cost was therefore borne by the family practitioner budget. The services of the homecare company and the recurring cost for the provision of ancillary supplies have been met from the budget of the health authority in which the child lives.

TRAINING AND COMMUNITY SUPPORT

Before discharge both parents were instructed by our nutrition nurse in the care of the feeding catheter and the safe delivery of the nutrients. Training takes two to three weeks during which time both parents are resident in the hospital. Nursing staff from the referring hospital and carers from nursery or primary school were also instructed in the emergency care of the central line. The specific points taught to the parents are listed in table 3. A home visit was made by our nutrition nurse to assess the suitability of the child's home for HPN. The child should

Table 2 Equipment needed for a child on HPN

- Intravenous infusion pump (leasing availability from homecare company with 4 hour backup service)
- Pump stand
- Dressing trolley (folding)
- Refrigerator (for storage of HPN bags)
- Intravenous giving sets
- Sterile clamps
- Dressing packs
- Chlorhexidine
- Syringes and needles
- Saline and heparinised saline flush
- Sharps' bins and bin bags (with clinical waste disposal service)
- Catheter caps
- Storage shelves (giving sets, dressing packs, etc)
- Mepore dressings (Mölnlycke)
- Adhesive tape
- Treatment area (usually in bedroom)
- 13 amp plug points
- Telephone
- Adequate plumbing facilities

Table 3 Points taught to both parents before child discharged home on HPN

- Hand washing technique
- Principles of asepsis:
  - Preparation of sterile field
  - Putting on sterile gloves
  - Drawing up solutions into syringe
- Catheter care:
  - Heparinisation and flushing catheter
  - Exit site care
- Infusion:
  - Priming of giving sets
  - Initiation/termination of infusion
- Care of parenteral nutrients
- Care of infusion pump:
  - Pump operation
  - Maintenance
  - Alarms
- Monitoring at home:
  - Urinalysis
  - Temperature taking if feverish
- Problem solving:
  - Temperatures
  - Accidental disconnection of line
  - Blockage of line
  - Air in line
  - Breakage/split catheter
  - Who to contact in an emergency (24 hours)

ideally have a bedroom to themselves with adequate space in the house for the storage of the ancillary items and nutrient solutions. A professional's meeting was arranged so that the general practitioner, health visitor, social services, and other community health care professionals were fully involved and were aware of the needs of the child and family once he or she was home. With four patients minor alterations were required to the family home to accommodate the HPN. All families in the UK have successfully applied for an attendance allowance.

MONITORING OF HPN

A summary of the monitoring regime used is shown in table 4. Where possible monitoring was shared with the local referring hospital.

DEVELOPMENT

We assessed the developmental progress of the children at the time of discharge and at home by serial assessment. All tests were carried out by the same clinical psychologist using tests appropriate for their age. The Griffiths's mental development scale was used in those under 3·8 years,[11 12] the Wechsler preschool and primary scale of Intelligence (WPPSI) for those under 6·5 years,[13] and the Wechsler intelligence scale for children revised (WISC-R) in the older children.[14] The Griffiths's score is presented as a general quotient (GQ) and the other scores as an intelligence quotient (IQ).

STATISTICS

A paired t test was used to compare height SD scores and the 95% confidence intervals (CI) are quoted.

Results

Of the 10 children who were discharged on home parenteral nutrition, eight are presently alive and well, one has moved to the USA after 2·7 years of follow up (patient 5), and one patient has died from the surgical complications of her underlying short gut syndrome (patient 6). Since discharge from hospital the patients have progress well with few complications, particularly over the last nine patient years when there have been no infective or nutritional complications in any of our patients. Of the eight well patients, seven remain on HPN while one child has been able to discontinue intravenous nutrition after 3·5 years of HPN (patient 4).

GROWTH AND NUTRITION

Before starting HPN all of the patient weights were within the normal range for age and all but one of the heights were within 2 SD of the mean for their age. One child who was chronically malnourished for many years before starting intravenous feeding (patient 8) had a height which was 5·13 SD below the mean. After the start of HPN all of the children have maintained their weight within the normal range and there has been a significant increase (mean of differences 0·837, 95% CI 1·53 to 0·143) in their SD score for height. This effect is most noticeable in the stunted patient where the growth velocity increased from 4·0 cm/year before starting HPN to 10·4 cm/year after. The growth results are summarised in fig 1.

Nutritional deficiencies occurred in the first patients discharged (patient 1–5) on HPN, but now with the improved formulation of feeding regimens and better monitoring we have experienced no nutritional complications in our patients over the last 15 patient years. Patient 1 was discharged on oral vitamin supplements but unfortunately these were not taken by the child, leading to the development of Wernicke's encephalopathy and in another with short gut syndrome (patient 5) deterioration in stool

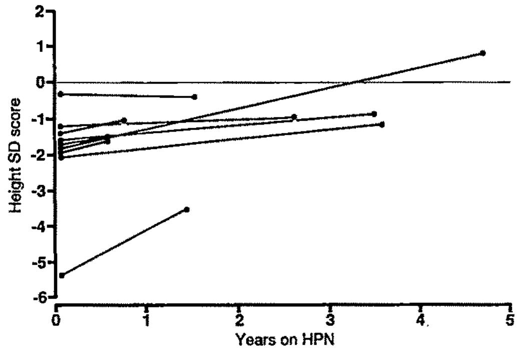

Figure 1 The change in height as measured by the SD score, over the period of HPN. Height unavailable for patient discharged to Italy.

Table 4 Investigations for the monitoring of HPN

Time		*Investigation*
Before discharge		All investigations shown below
4–6 Weeks	Anthropometry	Weight, height
	Haematology	Full blood count
	Biochemistry	Urea and electrolytes, calcium, magnesium, liver function tests, urine electrolytes
	Bacteriology (if indicated)	Urine culture, line site
3 Months	Haematology	Ferritin, clotting
	Biochemistry	Copper, zinc, selenium
6 Months	Haematology	Folate, vitamin B-12
	Biochemistry	Vitamin B-1, B-2, B-6, vitamin A, E, D
	If indicated	Aluminium, chromium, manganese, essential fatty acids
	Radiology	Liver ultrasound, chest radiography
1 Year	Cardiology	Echocardiography
	Psychology	Developmental assessment

losses resulted in zinc deficiency despite intravenous supplementation. The first five patients discharged developed subclinical selenium deficiency because their HPN did not contain any supplements.[15] In all cases the deficiencies were corrected with no long term sequelae for the children.

BIOCHEMISTRY

Despite the fact that some of the children had large stool losses of fluid and electrolyte it was possible in all cases to maintain a good balance. In one child (patient 6) who lost 1 litre of fluid and 150 mmol of sodium per day from a high jejunostomy, this was compensated for by appropriate additions to the intravenous feed.

It is well recognised that liver disease is frequently associated with long term intravenous feeding. In three patients (patients 6, 7, 10) the activity of aspartate aminotransferase was chronically raised above 100 IU/l (normal range <40 IU/l) and in the remaining patients the activity was maintained either within or just above the normal range. Only one of these three patients (patient 7) has undergone serial liver biopsy, which has shown evidence of mild non-progressive periportal fibrosis. No patients have had raised bilirubin concentrations at home, although the patient who died after abdominal surgery developed a cholecyst-enteral fistula, ascending cholangitis, and jaundice as a preterminal event. One infant has developed gall stones (patient 7) and has undergone a cholecystectomy. A second child (patient 9) had evidence of 'sludge' in the gall bladder that has subsequently resolved after increased enteral food tolerance.[16 17]

VENOUS ACCESS, LINE CARE, AND INFECTION

Venous access is always a limiting factor in the delivery of intravenous feeding and great care is required to extend the life of feeding catheters. Due to the care and dedication of the parents the average line life is 680 days with a range of eight to 1760 days.

The incidence of line sepsis is difficult to calculate as some septicaemic episodes may originate from the intestine. In six of the 10 children (patients 2, 3, 7, 8, 9, 10) no septicaemic episodes have occurred since discharge home, while a total of 19 episodes have occurred in the remaining four children (patients 1, 4, 5, 6: one pseudo-obstruction, two short gut, one congenital enteropathy). In 13 of these episodes an enteric organism was isolated from blood culture and *Staphylococcus epidermidis* and a streptococcus were responsible for the remaining case. The overall rate of septicaemia was one in 476 days.

Line infections were treated with intravenous antibiotics delivered through the line for 10 days. Where the patient became very unwell and/or the infection was not brought under control within 72 hours or recurred after the cessation of antibiotics the feeding catheter was removed and electively replaced three to seven days later. Redness at the entry site of the catheter to the skin tunnel occurred in most of the patients and settled, in all but one case (patient 4), with the topical skin application of chlorhexidine. In the latter case the line was removed.[18 19]

A total of nine lines have been replaced in five of the patients (patients 1, 3, 4, 5, 6). Five were removed because of catheter related sepsis, in one the line was damaged beyond repair, in another poor scar formation around the catheter cuff led to the line falling out, in one patient an innominate vein thrombosis precipitated catheter removal, and in one patient a catheter could not be unblocked.[20 21] In two patients with a blockage of the catheter hub, replacement of the hub using a Broviac repair kit allowed us to save the feeding catheter without resorting to replacement of the central line.

DEVELOPMENT

All of the children were within the normal range at the time of discharge, and while on HPN their development has progressed normally (fig 2). Specific delay in the development of speech was noted in four of the younger children and in three this corrected after discharge home. In the fourth patient (patient 4) speech therapy and treatment for middle ear disease has been required.

EDUCATION

All seven children of school age attend normal school. One child with an ileostomy (patient 1) goes to a normal school where extra help is available. Another child with speech problems (patient 4) as a consequence of a palatal defect and middle ear disease attends a normal school with a special language unit. A third child (patient 8) who missed prolonged periods of schooling before starting HPN requires some remedial teaching. Physical contact and games with other children were not restricted and some of the children go swimming with their central venous catheter protected by a clear waterproof film (for example, Tegaderm, 3M Healthcare).[22 23] The oldest child has recently sat his university entrance examinations.

FAMILY HOLIDAYS

All the families have been able to take a holiday with their child. This has inevitably meant taking the infusion pump and intravenous

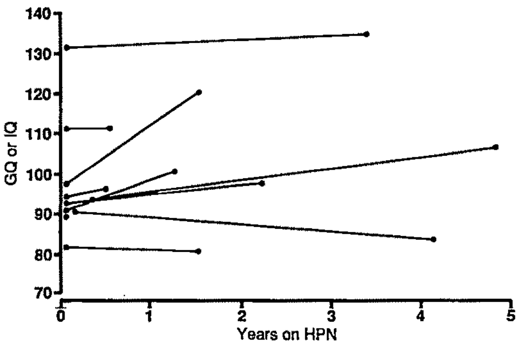

Figure 2 The development progress of the children while on HPN as expressed by their GQ or IQ. Developmental tests described in text. Incomplete data for patient who died.

nutrients with them and as a consequence most have gone by car and have stayed in self catering accommodation. We have, however, been able to arrange holidays in the USA and Sicily as the company that manufactures the HPN has subsidiaries throughout the world.

ORGANISATION

With seven of the eight British children their original general practitioners' (GP) agreed to prescribe the HPN. In one case a single handed GP was not prepared to take responsibility for the child at home and a new GP was found. The cost of the HPN solutions was £20 000–£25 000 per year but due to special dispensation from the Department of Health the GPs were not penalised. Difficulties in contacting the budget holder for community services has led to problems in arranging HPN. Because the referral hospital and the patient's home may be in different health authorities there was often considerable delay between a request being made and an agreement reached. On average it has taken three months to arrange for the discharge of a child on HPN, although this has ranged from between one month to discharge a child back to Italy to over 18 months to discharge a child home to a south London health district which has no community resources. We have found that most health authorities have no provision in their budgets for the care of children requiring long term medical treatment at home and as a consequence it may take some time for them to find the required funding. The community funding of the infusion pump and consumables cost £3000–£5000 per year.

Discussion

Our experience over the last five years would suggest that HPN is a safe and efficient means of delivering nutrients to children with chronic intestinal failure. The children are able to grow and develop normally at home with their families and apart from their gut disease they are essentially healthy normal children.

Many consider parenteral nutrition as highly dangerous and regard it as a treatment of last resort. This view stems from the time when nutrients were compounded by ward staff, venous access was poor, and as a result of poor sterile technique morbidity and mortality from sepsis were unacceptably high. The advances in knowledge regarding parenteral nutrition and its nursing care means that this is no longer the case and intravenous feeding should be considered at an early stage for the treatment of severe gastrointestinal disease. Although it is generally assumed that the medical care of a child requiring intravenous nutrition would be best carried out by trained staff in hospital, our study and a number of others show quite clearly that this is not the case and that well trained and supported parents are more than capable of performing this task at home.[1 2 4 5] Appreciably reduced line sepsis rates and prolonged line survival in home patients almost certainly relate to the consistent care the children receive from highly motivated parents and parallels similar findings in adult patients at home.[19] It is noteworthy that in two of our patients line infections occurred not at home but during brief hospital admissions for respite care.

Our data suggest that simple HPN regimens, which do not require the addition of intravenous supplements such as vitamins or trace metals at home, are likely to carry the lowest sepsis rates. This is illustrated by patient 1 who had six episodes of line sepsis in the first three years of HPN, at a time when trace elements were being added by her mother to the HPN, and no further episodes in the subsequent two years after these additions were made aseptically at the time of bag manufacture.

There was no relationship between the type of infective organism, the underlying intestinal disease, and the central venous catheter insertion site. The appreciable reduction in the incidence of septicaemia in HPN due to both Gram positive and Gram negative organisms, in patients in whom there had been no change in their underlying disease, strongly suggests that these infections were acquired from exogenous sources. This therefore casts doubt on the commonly held belief that septicaemia with an enteric organism, in a patient with a central venous catheter, must be due to endogenous spread from an intra-abdominal source.

With the improved life of central venous catheters it is likely that good venous access can be maintained in these children into adult life.

Hospital provides the young child with a very artificial environment, a lack of time for play, inconsistencies in handling, and infrequent mixing with children of a similar age and can result in the development of mild global development delay. Although with appropriate intervention it is possible to reduce this to a minimum, it is probably only once the child is returned to their home that they are able to meet their full potential.[10] Our study confirms this with normal somatic growth paralleled by normal neurological and intellectual development occurring after discharge from hospital.

All nutritional deficiencies occurred in the first five patients discharged home, and through a better understanding of the nutritional needs of these children we have not diagnosed any major deficiencies in the last three years.[24–26] However most routine biochemistry laboratories are unable to monitor all trace metals, water soluble vitamins, or essential fatty acids and as a consequence the need to send specimens to special reference laboratories is an added administrative and financial burden.

The parents are aware that the survival of their child is dependent on their skill in delivering the HPN and many find this a great burden. Some parents also feel trapped by the needs of the child but find that when they seek help from support agencies there is no understanding of the medical problems of the child or the social or emotional needs of the parents. Despite these problems all the parents feel that caring for their child at home is very rewarding and infinitely preferable to the child remaining in hospital. However the group of patients we describe here is highly selected and where a child has multiple organ failure or the family or medical services are unable to implement intravenous feeding at home, long periods in hospital may be unavoidable.

The greatest difficulty and cause of delay in arranging HPN is in agreeing the financial arrangements. In the USA the move toward the early institution of HPN in children with chronic intestinal failure has been driven largely by financial considerations and by the realisation that children requiring parenteral nutrition progress better at home from a nutritional and psychological viewpoint than those children who remain in hospital. This is further facilitated by the many commercial homecare companies who are able to manufacture the parenteral feeds and help train and support the parents at home. As the cost of health care in the USA is largely financed through medical insurance there are real incentives for the treatment of chronic problems at home rather than in hospital.

In the UK it costs approximately £100 000 each year to keep a child in hospital to receive intravenous nutrition against a cost of £20 000–£30 000 to receive the same treatment at home. Unfortunately, as a result of the budgetary arrangements within the National Health Service, the small number of homecare companies, and the poor level of development of community services, the incentives to send these children home do not exist and as a consequence the arrangement of HPN is difficult. The lack of any proper central funding for HPN in either children or adults means that the financial burden of funding this form of treatment must be borne by the family practitioner budget and the community budget of the local health authority. Unfortunately this is often seen as an added burden rather than as a large overall financial saving to the health service.

Because of these delays and difficulties children with conditions such as the short gut syndrome who might benefit from a short period (three to six months) of HPN while their intestine is adapting, require to remain in hospital at great expense to the health service. If arrangements for HPN could be made more swiftly, many of these patients would benefit from an early hospital discharge.

We have relied very heavily on the services of a commercial homecare company to arrange for the formulation and delivery of the HPN to our patients. Where a unit is caring for children on HPN who are all living close to their hospital there may be attraction in providing the whole service from local resources. We find that with patients scattered all over southern England, the homecare company is able to maintain consistent stock levels of supplies, take care of much of the administration, and continues to provide a service when the patient moves house or goes on holiday and have even arranged for the manufacture of HPN bags in other countries when the children go abroad on holiday.

For children with severe gastrointestinal disease unfortunate enough to be dependent on intravenous nutrition, HPN offers the prospect of a good quality of life with prolonged survival. Many children are likely to benefit from this treatment but until community services become better developed and funding arrangements within the health service more flexible it is likely that many children will continue to languish in hospital. Our study shows that this treatment is not only cheaper to the health service but offers the child the prospect of reduced morbidity with normal growth and development and a quality of life which allows them to fulfil their true potential.

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A biotinidase K_m variant causing late onset bilateral optic neuropathy

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Abstract

A patient with a newly recognised variant of biotinidase deficiency presented with acute loss of vision at the age of 10 years. Progressive bilateral optic neuropathy, spastic paraparesis, and a predominantly motor type neuropathy developed over the next five years. Metabolic investigations revealed biotin depletion causing multiple carboxylase deficiency. The basic defect was a biotin recycling disorder due to a mutant biotinidase with residual activity of 4·4% assayed routinely. Biocytin excretion in urine was only slightly increased. Further investigations on plasma biotinidase revealed biphasic kinetics with two different reduced values for maximum reaction velocity (V_{max}) and two for the Michaelis constant (K_m), one being almost normal and the other considerably raised. In contrast to this patient, two age matched children with partial biotinidase deficiency (2·8% and 2·9% of normal), but with a normal K_m for biocytin, remained asymptomatic. After six months of oral substitution with 10 mg biotin per day the coecocentral and peripheral scotomata regressed, the pyramidal signs in the lower limbs disappeared, and further progression of the motor neuropathy arrested.

We conclude that the differential diagnosis of unexplained bilateral optic neuropathy of juvenile onset, particularly when associated with upper and lower motor neuron disease, should include biotinidase deficiency.

Biotinidase deficiency represents an autosomal recessive inborn error of biotin metabolism causing late onset, biotin responsive, multiple carboxylase deficiency.[1–3] Biotinidase acts by recycling biotin through liberation from biocytin (ε-aminobiotinyl lysine) or from short biotinyl peptides formed during proteolytic degradation of the biotin dependent carboxylases: propionyl-CoA carboxylase (PCC; EC 6.4.1.3), 3-methylcrotonyl-CoA carboxylase (MCC; EC 6.4.1.4), pyruvate carboxylase (PC; EC 6.4.1.1), and acetyl-CoA carboxylase (ACC; EC 6.4.1.2.). In biotinidase deficiency biocytin is lost in urine[4] leading to progressive biotin depletion and subsequently to multiple carboxylase deficiency.[3]

Biotinidase deficiency in its classical form usually presents during the first year of life with variable neurological signs (hypotonia, seizures, ataxia), dermatitis, alopecia, and recurrent infections. Metabolic acidosis and organic aciduria due to decreased activities of the biotin dependent carboxylases are inconsistently found. Despite rapid clinical and biochemical improvement after treatment with pharmacological doses of biotin, neurological damage such as sensorineural hearing loss, optic atrophy, ataxia, and mental retardation has been reported to persist.[3 5 6] Since the introduction of neonatal screening a number of children with partial biotinidase deficiency have been detected of whom most have remained clinically asymptomatic.[7 8] In the present paper a new variant of biotinidase deficiency with delayed onset of symptomatology is described. In addition the effect of biotin treatment will be presented.

Case report

The patient was the single child of healthy non-consanguineous parents born in Poland after an uneventful pregnancy and delivery; his birth weight was 3250 g. Neurodevelopmental progress and growth in the first decade were reported to have been completely normal. At the age of 10 years the patient complained of acute visual loss during the course of a 'flu'-like illness. Bilateral optic atrophy was found and visual acuity was decreased to 20/100 with small bilateral coecocentral scotomata (see fig 1, upper section). Computed tomography, electroencephalography, and routine laboratory investigations gave normal results. He was treated empirically with parenteral vitamin B-12 but his vision continued to deteriorate. From the age of 14 he complained of fatigue, particularly after exercise, with weakness in the hands particularly when opening boxes or unscrewing bottles.

Upon referral at the age of 15 years visual acuity was 20/200 on the right and 20/400 on the left and a mixed colour discrimination defect of red-green and blue-yellow type was found. Both optic discs showed appreciable temporal pallor with increased retinal transparency along the temporal arcuate fibre bundles. Coecocentral as well as peripheral scotomata had become enlarged (see fig 1, middle section). Other ocular findings were bilateral ptosis and mild chronic conjunctival injection. There was intense perspiration of the extremities but no signs of organ failure, alopecia, or dermatitis.

Psychometric assessment showed a full scale intelligence quotient of 90. There were no cranial nerve abnormalities apart from mild ptosis and lack of facial expression. In the upper limbs considerable thenar muscle wasting with finger fasciculation was observed and grip was very weak. In the lower limbs there was distal muscle wasting with bilateral pes cavus and hammer toes. His gait was stiff and shuffling but he was not ataxic. Tendon reflexes in the

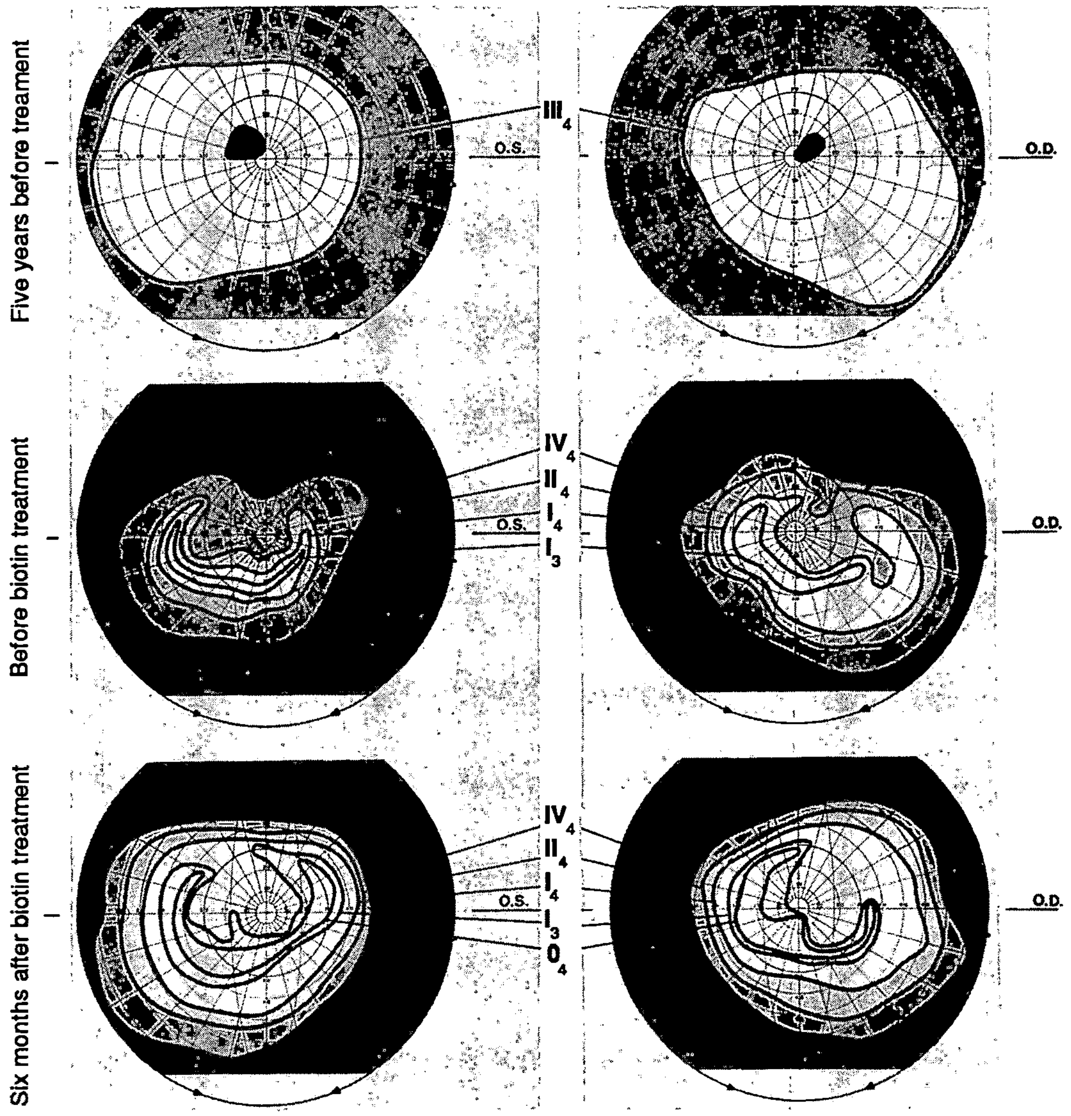

Figure 1 Visual fields. Top: initial examination at the age of 10 years in Poland showed an enlarged blind spot extending into the central visual field. Middle: at the age of 15 years the visual fields demonstrated enlarged coecocentral scotomas with wedgelike extensions into the temporal visual field breaking through to the periphery. Bottom: six months after treatment with 10 mg biotin/day the visual fields had improved with reduction of depth and extent of the coecocentral scotomas and opening up of the peripheral visual field borders. The roman numbers from 0 to IV represent the identification borders for differently sized object, from the size of 1/16 mm^2 (O) to 16 mm^2 (IV) respectively. Increasing light intensity is indicated by arabic numbers from 1 to 4. The most important scotomas have been shaded by a grey-white scale.

upper limbs were normal but in the legs they were symmetrically exaggerated with extensor plantar responses and ankle clonus. There was slight reduction of vibration sense distally in the lower limbs.

Electroneuromyography in median, tibial, and common peroneal nerves was consistent with severe neuroaxonal denervation. Motor and sensory conduction velocities were normal. Sensory nerve action potentials derived from the sural and median nerve were normal. Audiometry, brain stem and sensory evoked responses were also normal. The normal electroretinogram excluded any defects at the level of the retinal photoreceptor-ganglion cell unit. The pattern visual evoked response (stimulus size=80 minutes of arc) was extinguished on the right and equivocal on the left. Brightness stimuli showed plump responses with diminished amplitudes and prolonged latencies. The findings on electroretinography and from evoked visual responses suggested severe axonal fibre loss and conduction disturbance.

In peripheral nerve, measurements of neurofilament density indicated shrinking of axons of myelinated nerve fibres but the ultrastructure of non-myelinated nerve fibres appeared normal. A muscle biopsy specimen showed light microscopic changes indicative of a slowly progressive neurogenic muscle atrophy.

Despite normal macroscopic appearance of skin and hair, microscopy of a skin biopsy specimen showed chronic inflammatory changes characteristic of chronic dermatitis. On light microscopy a conjunctival biopsy specimen showed extensive inflammatory changes consistent with chronic conjunctivitis.

Computed tomography, magnetic resonance imaging, electroencephalography, cardiac function, analysis of protein in the cerebrospinal fluid, and routine laboratory tests gave normal results. The first screening of urinary organic acid excretion showed a moderately raised excretion of 3-OH-isovaleric acid and a trace of 3-OH-propionate (courtesy of Dr Lehnert, Freiburg). A colorimetric screening test for biotinidase was positive. Neurological assessment, ophthalmological and neurophysiological examination in both parents gave normal results. Other family members were not available for ophthalmological studies.

EFFECT OF BIOTIN TREATMENT

Before detection of the metabolic inborn error the patient's diet was normally balanced and was lacking food substances rich in biotin. After confirmation of partial biotinidase deficiency daily substitution with 10 mg biotin was started. After six months on biotin treatment the coecocentral scotomata regressed and peripheral visual fields showed recovery to near normal (fig 1, bottom section). Colour discrimination had also improved. These clinical findings could be substantiated by examination of his visual evoked responses. While pattern visual evoked response (representing the central 5–10° of arc) remained unaltered, the brightness stimuli demonstrated appreciable recovery of amplitudes and latencies. Subjective improvement with less fatigue over the daytime and after exercise was reported by the patient. After biotin supplementation further deterioration of the motor neuropathy arrested. Eight months after biotin supplementation the pyramidal signs in the lower limbs had disappeared.

Special biochemical studies

METHODS

Biochemical data obtained in the patient were compared with those of two age matched girls who had residual biotinidase activities of 2·8% and 2·9% of mean normal (table 1). In contrast to the patient these 15 year old girls appeared perfectly healthy and were neurologically normal.[8]

Informed consent was obtained from the parents and patient before the samples of blood, cerebrospinal fluid, and urine were collected. Organic acids were quantified using gas chromatography/mass spectrometry. Biotin concentrations were determined in plasma and urine samples by a microbiological assay using *Lactobacillus plantarum*-ATCC 8014.[9] Biocytin concentrations in urine were measured by a modified high performance liquid chromatography (HPLC).[4 8] The activities of biotin dependent mitochondrial carboxylases (PCC, MCC, PC) in lymphocytes were measured before and after in vitro activation of apocarboxylases with excess of biotin as described previously.[10] ACC activity was assayed in lymphocytes by measuring the citrate activated incorporation of [^{14}C]-bicarbonate into malonyl-CoA.[11] Biotinidase activity in plasma was measured colorimetrically using 0·15 mmol/l biotinyl-p-aminobenzoate as substrate.[12] Kinetic studies on biotinidase were performed by a sensitive HPLC method that uses the natural substrate biocytin.[8] Plasma from one of the girls with partial biotinidase deficiency was analysed in the same set of assays as that of the patient. To measure the maximum reaction velocity ($\dot{V}_{max}$) and Michaelis constant (K_m) for biotinidase initial velocities were measured using several biocytin concentrations varying from 0·00125 to 2·0 mmol/l assay mixture. The results were plotted using Eadie-Hofstee reciprocal plots, from which the respective $\dot{V}_{max}$ and K_m values were derived.

Results

Before biotin treatment organic acid analysis showed only moderate abnormalities in urine with a slight rise of 3-OH-isovalerate of 30 μmol/mmol creatinine (normal 8±4 μmol/mmol) and a trace of 3-OH-propionate. Plasma concentrations of 3-OH-isovalerate (9 μmol/l), 3-OH-propionate (12 μmol/l), and 3-OH-butyrate (44 μmol/l) were also moderately increased. The latter organic acids, except for 3-OH-butyrate, are not normally detectable in plasma. However, in cerebrospinal fluid the concentration of 3-OH-isovalerate was 250 μmol/l, that is, 27 times the concentration in plasma. Plasma and cerebrospinal fluid lactate and pyruvate were all within the normal range. Tiglylglycine, methylcitrate, and 3-methyl-crotonylglycine were not detected in any of the body fluids investigated. Prompt response to biotin supplementation was shown after 24 hours by normalisation of 3-OH-isovalerate concentrations in plasma (1 μmol/l) and urine (9·7 μmol/mmol creatinine). After four weeks a repeated lumbar puncture showed return of the 3-OH-isovalerate

Table 1 Biotinidase activity in plasma and kinetic parameters for plasma biotinidase calculated from Eadie-Hofstee reciprocal plots presented in figure 2

Subject	*Activity (nmol/min/ml plasma)**	*Kinetic parameters***		*Factors†*
		$\dot{V}_{max}$ (nmol/min/ml plasma)	*K_m (×10^{-6} mol/l)*	
Patient	0·275	$0·101=\dot{V}_{max1}$ $2·38=\dot{V}_{max2}$	$5·56=K_{m1}$ $1000=K_{m2}$	F=2495 $p<0·0001$
Girls with partial biotinidase deficiency:				
(1)	0·181	0·206	3·22	r=−0·984
(2)	0·172	0·135	3·27	r=−0·974
Patient's mother	6·76	7·35	3·44	r=−0·984
Patient's father	5·71	5·59	2·38	r=−0·966
Normal controls:				
Mean (SD)	6·24 (0·92)	5·86 (1·6)	3·06 (0·78)	
Range	4·59–8·25 (n=23)	3·60–8·50 (n=10)	2·10–4·88 (n=10)	

*Routine colorimetric method: biotinyl-para-aminobenzoate as substrate 0·15 mmol/l assay mixture. **HPLC method: biocytin as substrate (for details see text and reference 4).

†r=Pearson correlation coefficient for linear regression lines using the least square method. F=F value as measure of significance of the curve fitting.

concentration in the cerebrospinal fluid to the normal range. Plasma biotin concentrations before biotin treatment were undetectable (table 2). The mitochondrial carboxylase activities in lymphocytes of the patient were appreciably decreased (12–20% of mean normal values), and ACC activity was within the normal range. Biotin responsiveness could be demonstrated in vitro by the normalisation of the carboxylase activities after preincubation with excess biotin. In the two girls with partial biotinidase deficiency the mitochondrial carboxylases were only moderately decreased to 30–58% of mean normal values.

Compared with controls and the girls with partial biotinidase deficiency the urinary biocytin excretion in the patient before and during biotin treatment was slightly raised, but was only 10% compared with the mean of biocytin excretion determined in 11 patients with complete biotinidase deficiency (mean (SD): 24·9 (8·3) nmol/mmol creatinine, range: 10·6–36·6).

Table 2 Biotin concentrations in plasma and biotin and biocytin concentrations in urine

Subject	*Biotin treatment*	*Plasma biotin (nmol/l)**	*Urine (nmol/mmol creatinine)*	
			Biotin	*Biocytin*
Patient†	Nil	<0·4 (n=4)	0·67–3·6 (n=5)	0·87–2·4 (n=5)
	10 mg/day	67·5	308–3503 (n=8)	0·92–2·4 (n=8)
Girls with partial biotinidase deficiency†:				
(1)	Nil	0·66, <0·4	2·4–3·5 (n=3)	0·29–0·58 (n=3)
(2)	Nil	0·69, <0·4	3·0–8·0 (n=3)	0·26–0·33 (n=3)
Normal controls:				
Mean (SD)		1·77 (0·72)		
Range		0·90–4·14 (n=71)	2·7–141 (n=71)	0·05–0·53 (n=17)

*Limit of detection 0·4 nmol/l.
†The numbers in parentheses indicate the number of tests performed on different samples from the same patient.

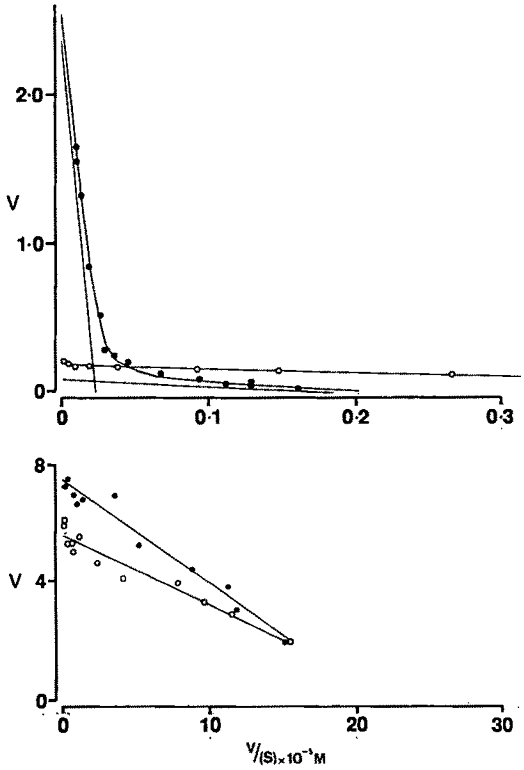

Figure 2 Eadie-Hofstee reciprocal plots of the plasma biotinidase assay data. The ordinate with the symbol V indicates the biotinidase enzyme kinetic activity in nmol/min/ml plasma. The abscissa represents the value for kinetic activity divided by the used biocytin substrate concentration in 10^{-5} mol/l. The upper part shows the data for the patient (closed circles) and for one of the age matched girls (1) with partial biotinidase deficiency (open circles). The lower graph shows the data for the mother (closed circles) and father (open circles) of the patient. The plots were analysed either by computed least square fit (patient non-linear plot) or by the least square method (linear plots). The kinetic parameters calculated are listed in table 2. For details see text.

Biotinidase activity in the plasma of the patient measured by the colorimetric method was decreased to 4·4% of mean normal (table 1). Surprisingly, biotinidase activities in plasma of the parents were within the normal range (table 1).

The Eadie-Hofstee plots obtained from the kinetic analysis of biotinidase are shown in fig 2 and the calculated K_m and $\dot{V}_{max}$ values are listed in table 1. The girls with partial biotinidase deficiency as well as the parents of the patient showed linear plots by the least square method. The kinetic parameters were within the normal range except that the girls with partial deficiency had a decreased $\dot{V}_{max}$. For the patient the plot was bilinear and could be resolved into two lines by computed least square fit according to the statistical methods used for resolving non-linear Scatchard plots.[13] The data correlated best with the assumption of two different enzyme molecules with different kinetic properties ($F=2495$, $p<0·0001$). The first K_m with the lower $\dot{V}_{max}$ of 1·7% of mean normal was only slightly above the normal range. The second K_m value with the $\dot{V}_{max}$ of 41% of mean normal was 326 times the mean normal value. In the patient this kinetic pattern was reproducible in different fresh and stored plasma samples. Mixing experiments failed to show any inhibitory factors in his plasma.

Discussion

This patient presented with acute onset optic neuropathy, spastic paraparesis, and a predominantly motor type neuropathy of the neuroaxonal type. At first the typical neuro-ophthalmological findings suggested Leber's hereditary optic neuropathy, most commonly a maternally inherited disease due to a mitochondrial DNA mutation.[14 15] However, in our patient there was no evidence for maternal transmission. Other distinguishing features were the presence of mild conjunctivitis and dermatitis, the latter being evident only on light microscopy. Our studies showed that the underlying defect in our patient is a biotin recycling disorder caused by a mutant biotinidase with biphasic kinetics. Phenotypic expression of classical biotinidase deficiency is highly variable; clinical features commonly include seizures, hypotonia, ataxia, breathing problems, hearing loss, optic atrophy, developmental delay, skin rash, conjunctivitis, and alopecia.[3 5 6] Acutely ill patients may present with fungal infections probably due to abnormal immunoresponse. Most, but not all, symptomatic children exhibit metabolic acidosis and organic aciduria. The age of onset in 38 classical cases with biotinidase deficiency varied from 1 week to 2 years with a median age of 3 months.[3]

In our patient the first symptom was acute onset of bilateral optic neuropathy at the much later age of 10 years followed by other neurological abnormalities. He had no significant organic aciduria and macroscopic skin or hair abnormalities were absent. Another surprising finding was the absence of hearing abnormalities, whereas the majority of symptomatic patients who were diagnosed late suffered from hearing loss. It should be emphasised that the history of our patient did not show any evidence of increased dietary intake of free biotin that might explain the delayed onset of clinical symptoms. Biotin treatment in our patient led to considerable improvement of the optic neuropathy, disappearance of pyramidal signs, and arrest of progression of the neuropathy. However the long term outcome is not yet known. In other patients with delayed onset of biotin supplementation there was prompt reversal of the metabolic derangement and of most clinical symptoms with the exception of optic atrophy and hearing abnormalities which persisted in some of them. The selective vulnerability of the central nervous system in biotinidase deficiency has been observed previously in a single case resembling Leigh's disease. This phenomenon was attributed to earlier depletion of biotin stores in the brain than in other tissues,[16] which was confirmed by postmortem enzyme studies of brain, liver, and kidney.[11] In the present patient the 27-fold higher 3-OH-isovalerate concentration in cerebrospinal fluid compared with plasma supports this hypothesis.

The relationship between the unusual clinical course in our patient and the enzymatic findings is not understood. To our knowledge similar biphasic kinetics have never been observed in plasma of other patients with complete or partial biotinidase deficiency. In our patient biocytin excretion was significantly lower than in patients with complete biotinidase deficiency indicating a considerable recycling of biotin. On the other hand, biotin recycling in our patient was more severely compromised than in the girls with similar residual biotinidase deficiency but a normal K_m value. This is reflected by his 2–4 fold higher excretion of biocytin compared with the girls with partial deficiency.[8] The absence of symptoms in these two 15 year old girls suggests that residual biotinidase activity as low as 2–3% with normal K_m maintains biotin concentrations high enough to result in sufficiently active carboxylases avoiding pathogenic consequences.[8] However, in our patient similar residual activity in combination with an abnormal K_m does not allow sufficient recycling of biotin to prevent neurological abnormalities.

Further investigations are needed to clarify the molecular basis of the biphasic kinetics of this biotinidase K_m variant. It is of interest that biotinidase activity in the patient's parents was normal in contrast to the intermediate activity observed in parents of patients with complete or partial biotinidase deficiency.[7 8]

In conclusion we recommend looking for K_m variants in biotinidase deficient patients with an unusual clinical course. Disorders of biotin metabolism should be included in the differential diagnosis of patients presenting with unexplained sudden visual failure as early detection and biotin supplementation will prevent visual or neurological deterioration. The basic screening for disorders of the biotin cycle should include both urinary organic acid analysis as well as the colorimetric biotinidase assay on plasma by using three different substrate concentrations. Testing of biotinidase activity at different substrate concentrations will roughly detect biotinidase K_m variants.

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Beta glucuronidase and hyperbilirubinaemia in breast fed infants of diabetic mothers

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Abstract

A prospective study was performed comparing bilirubin concentrations in 10 breast fed term infants of diabetic mothers (IDM) to those of 10 breast fed normal term infants. The β-glucuronidase concentrations in serum and breast milk were assayed in the respective mothers. Significantly higher bilirubin concentrations were noted in the IDM group. Serum and breast milk β-glucuronidase concentrations were significantly higher in diabetic mothers as compared with those of non-diabetic mothers. We suggest that the high concentration of β-glucuronidase in breast milk of diabetic mothers is an additional important cause leading to hyperbilirubinaemia in their breast fed infants.

Hyperbilirubinaemia is observed more frequently in infants of diabetic mothers (IDM) than those of non-diabetic mothers. Although a number of hypotheses have been suggested, the pathogenesis remains uncertain.[1] To our knowledge, there are no previous reports describing the relationship between breast feeding and hyperbilirubinaemia in IDM.

Neonatal intestinal β-glucuronidase antagonises the net clearance of bilirubin by increasing enterohepatic circulation causing increased serum bilirubin.[2] In 1986, Gourley and Arend reported that the β-glucuronidase present in maternal milk is an important factor in breast milk jaundice.[3] In a previous report higher values of serum β-glucuronidase were found in pregnant diabetic women in comparison with non-diabetic women.[4]

In the present study we have examined the hypothesis that the increased concentration of breast milk β-glucuronidase in diabetic mothers may be an additional cause of hyperbilirubinaemia in their breast fed infants.

Patients and methods

Ten breast fed IDMs and their mothers were examined. All the diabetic mothers were insulin dependent, classes B and C, according to White's classification of maternal diabetes.

A group of 10 breast fed term infants, of appropriate weight for gestational age, and their mothers served as a control group. All the infants in the study were born by spontaneous vaginal delivery. Babies with blood incompatibilities, sepsis, birth asphyxia, bruising, cephalhaematoma, and other obvious causes of neonatal jaundice were excluded. IDMs with hypoglycaemia treated with dextrose fluids orally or intravenously were not included in the study.

On the third postpartum day maternal serum and breast milk were collected and analysed for β-glucuronidase. Breast milk was collected with a manual pump and immediately deposited in an iced container. All serum and breast milk samples were kept at −20°C and thawed at room temperature before assaying.

The β-glucuronidase activity was assayed with phenolphthalein mono-β-glucuronic acid substrate (Sigma kit No 325) and was expressed in Sigma units at 56°C.

On the third day of life bilirubin was measured in the serum of all babies studied. This was done spectrophotometrically by the Advanced Bilirubin Stat-Analyzer Photometer model BR2.

Statistical analysis was performed using Student's *t* test.

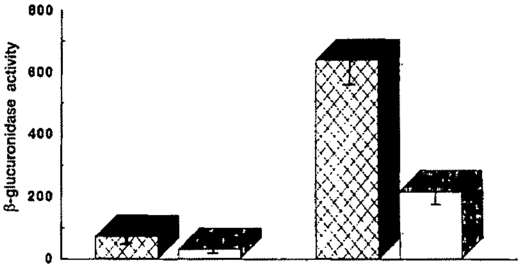
Results

Mean (SD) serum β-glucuronidase concentration was significantly higher in diabetic mothers (71·5 (23) Sigma/units) as compared with non-diabetic mothers (30 (10) Sigma/units) ($p<0·0005$, figure).

In both diabetic and non-diabetic mothers, breast milk β-glucuronidase concentration was significantly higher (640 (205) and 216 (70) Sigma/units, respectively) than in the serum ($p<0·005$, figure).

Birth weight was not significantly different between the IDMs (3760 (800) g) and the control group (3400 (300) g). The packed cell volume at the age of 24 hours was not significantly different between the IDMs (54·3 (9·4)) and the controls (53·3 (6·6)).

The mean (SD) peak of serum bilirubin concentration on the third day of life was significantly higher in IDMs (210·3 (107·7) μmol/l) in comparison with controls (123·0



Mean serum and breast milk β-glucuronidase concentrations expressed in Sigma/units in diabetic and non-diabetic mothers.

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(66·7) μmol/l $p<0·005$). None of the normal (control) infants was treated with phototherapy in contrast to 50% treated in the IDM group. None of the IDM group had phototherapy before bilirubin estimation on day 3.

Discussion

Hyperbilirubinaemia is frequently observed in IDM.[5-8] Although several mechanisms have been proposed to explain this clinical finding, the pathogenesis of hyperbilirubinaemia remains uncertain. The jaundice observed in the IDM was often attributed to biochemical immaturity of the liver of the IDM. Several studies have analysed morbidity carefully, according to gestational age, and have rejected this concept.[9-12] The increased incidence of Coombs' positive ABO incompatibilities in IDMs has not been confirmed either.[5] Polycythaemia frequently observed in IDMs may well be the most important factor associated with hyperbilirubinaemia. Venous packed cell volume above 0·65 has been observed in 20% to 40% of IDMs. Presumably the major stimulus for the enhanced red cell production is a state of relative hypoxia in utero.[9] To our knowledge this is the first report which describes the association between breast feeding and hyperbilirubinaemia in IDMs.

The association between breast milk feeding and neonatal jaundice was first described in 1963.[13] Recent studies have documented an increased incidence of hyperbilirubinaemia in breast fed infants during the first week of life.[14-18] Earlier studies reported that the onset of breast feeding jaundice occurred only at the end of the first week of life.[19 20] Some studies have attributed breast milk jaundice to the inhibition of hepatic uridine diphosphate glucuronyl transferase by the steroid pregnane 3α,20β-diol[21 22] or to the increased concentration of lipoprotein lipase and non-esterified long chain fatty acids in human milk.[23] Recently, Gourley and Arend reported the β-glucuronidase in maternal milk is an important factor facilitating intestinal reabsorption of bilirubin in breast fed infants, thus increasing the concentration in the enterohepatic circulation.[3]

Previous studies reported higher values of serum β-glucuronidase in pregnant diabetic women in comparison to non-diabetic ones.[24] We found significantly higher concentrations of serum β-glucuronidase in diabetic mothers in comparison with non-diabetic ones, thus delivery does not have an immediate direct effect on decreasing the serum β-glucuronidase value. Our finding is in accordance with that of Gaffiney *et al* confirming that concentrations of β-glucuronidase in breast milk are much higher than those in the serum.[25] As the concentration of β-glucuronidase was significantly higher in the breast milk of diabetic mothers, we assume that the amount in breast milk is in direct relationship with that in the serum. Because no significant differences were noted in the birth weight, packed cell volume, ABO and Rh incompatibility, and abnormal thyroid or liver function in IDMs compared with controls studied, we suggest that the significantly higher serum bilirubin concentration observed in the IDMs may be attributed to the higher concentrations of β-glucuronidase in maternal milk.

In conclusion we suggest that the higher concentrations of breast milk β-glucuronidase in diabetic mothers may be an additional important cause leading to hyperbilirubinaemia in the breast fed IDMs by enhancing the amount of bilirubin in the enterohepatic circulation.

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Axillary and rectal temperature measurements in infants

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Abstract

Rectal and axillary temperatures were measured during the daytime in 281 infants seen randomly at home and 656 at hospital under 6 months old, using mercury-in-glass thermometers. The normal temperature range derived from the babies at home was 36·7–37·9°C for rectal temperature and 35·6–37·2°C for axillary temperature. Rectal temperature was higher than axillary in 98% of the measurements. The mean (SD) difference between rectal and axillary temperatures was 0·7 (0·5)°C, with a range of 3°C. When used in hospital to detect high temperature, axillary temperature had a sensitivity of 73% compared with rectal temperature. This is too insensitive for accurate detection of an infant's high temperature. Rectal temperature measurement is safer than previously suggested: perforation has occurred in less than one in two million measurements. If an infant's temperature needs to be taken, rectal temperature should be used.

Body temperature is one of the commonest clinical signs used to determine whether a child is ill.[1,2] Surprisingly, there are little data to define a normal range in babies, as most studies have reported on ill babies.[3–5] Although rectal temperature is the measurement used in physiological studies[6–8] and for the management of seriously ill children,[9] axillary temperature is considered by some to be accurate enough for normal clinical practice.[3,10] Only two studies have analysed the accuracy of axillary compared with rectal temperature measurements in terms of sensitivity and specificity and they looked at small numbers of ill children.[4,5]

This paper endeavours to determine the normal daytime range for axillary and rectal temperature for infants in the first six months of life and assess the evidence for using an axillary or rectal temperature measurement.

Methods

During one year 298 full term babies were randomly selected from the birth register in Cambridge and seen at home in the first six months of life, evenly across the seasons. At the same time 709 babies of similar age were enrolled when they were presented to hospital for assessment of an acute problem. Twenty seven were seen in Cambridge and 682 at the Royal Children's Hospital, Melbourne, Australia. This was part of a much larger study to determine the importance of symptoms and signs of illness in babies under six months old.[10,11]

Rectal and axillary temperatures were measured using standard nursing procedures with mercury-in-glass thermometers. Rectal temperature was measured by inserting the thermometer approximately 3 cm past the anal margin and held in place for at least one minute, or until the temperature stopped rising. The axillary temperature was read after the thermometer had been in place for at least three minutes. Measurements were made between 8 00 am and 8 00 pm. In hospital the routine temperature taken by the admitting nurse was used. For the purpose of this study both axillary and rectal temperatures were measured in each baby. The data obtained represent temperatures taken in clinical practice rather than for a physiological study.

The data were analysed using the χ^2, Pearson's correlation coefficient, and the Bland–Altman analysis[12] for comparing two measurements.

Permission for this study was given by the Cambridge District Health Authority ethics committee and the Royal Children's Hospital ethics committee.

Results

REFERENCE RANGE FOR NORMAL TEMPERATURE

Of 298 babies seen on a randomised basis at home 281 had both rectal and axillary temperatures measured. The results from these babies were used to determine the reference range (mean, 2 SD) for normal daytime temperature. The mean (SD) for rectal temperature was 37·3 (0·35)°C with a range from 36·7–37·9°C. The mean (SD) axillary temperature was 36·4 (0·42)°C with a range from 35·6–37·2°C. The empirical 95% confidence interval for axillary and rectal temperature was identical to the value for 2 SD either side of the mean.

Figures 1A and 1B are scattergrams of rectal and axillary temperatures, where both were obtained, for babies at home and babies in hospital.

THE DIFFERENCE BETWEEN AXILLARY AND RECTAL TEMPERATURE

The mean (SD) for the difference between axillary and rectal temperatures at home was 0·8 (0·5)°C, at hospital 0·6 (0·4)°C and for both data sets combined 0·7 (0·5)°C. Figure 2 shows a Bland–Altman analysis for the difference between each pair of temperature readings where the difference is plotted against the average of the rectal and axillary temperatures for the home and hospital babies combined. This analysis does not assume that one measurement is more accurate than the other. The difference between the two temperatures may vary by up to 3°C (see also fig 1). The difference was only poorly correlated with the height of body temperature both at home (r=−0·13) and in hospital (r=0·21).

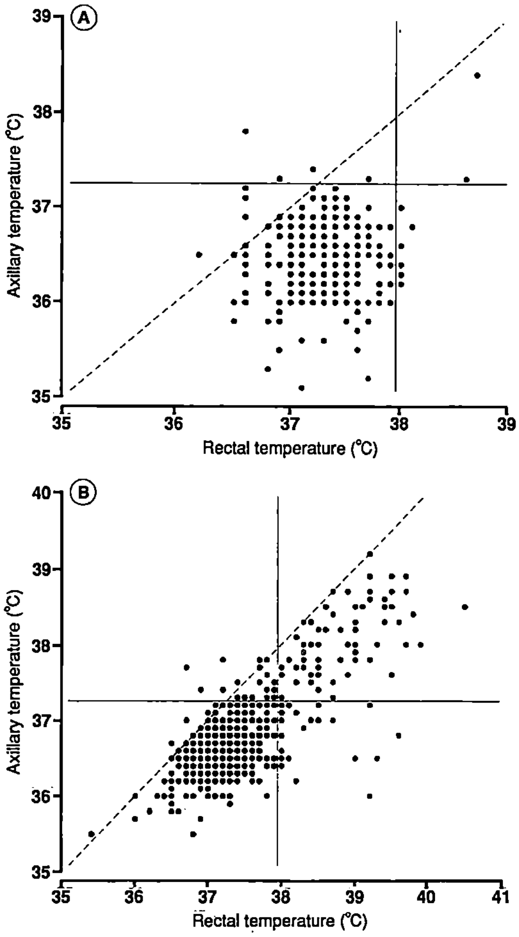

Figure 1 Scattergram of rectal and axillary temperature pairs from (A) babies at home (n=281) and (B) babies in hospital (n=656). The diagonal dotted line is the line of identity. The vertical solid line is the upper limit of normal (mean +2 SD) for rectal temperature. The horizontal solid line is the upper limit of normal for axillary temperature. Higher values are defined as fever. Some points represent more than one case.

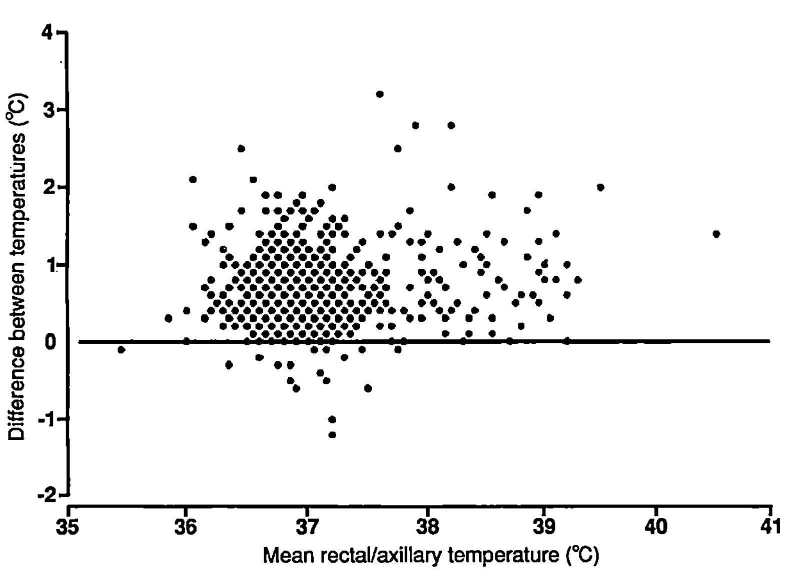

Figure 2 A scattergram of the difference between each rectal and axillary temperature measurement plotted against the average of each pair of temperatures for the home and hospital babies combined (n=937). The horizontal line indicates zero difference. Some points represent more than one case.

DEFINITION OF A HIGH TEMPERATURE

A high temperature is defined for this study as a temperature higher than 2 SD above the mean from the babies seen randomly at home. Thus a high rectal temperature is greater than 37·9°C and a high axillary temperture is above 37·2°C.

There is no 'gold standard' for measuring true body temperatures. However, rectal temperature was found to be a more precise measurement of body temperature for two reasons. The higher temperature is more likely than a lower one to be nearest the true body temperature, and rectal temperature was higher than axillary temperature in 917/937 (98%) of the babies. Rectal temperature was a more precise measurement, having a smaller SD than axillary temperature. Rectal temperature can therefore be considered to be the best reference measurement available for the detection of high temperatures.

IS AXILLARY TEMPERATURE LIKELY TO MISS HIGH TEMPERATURES DETECTED BY RECTAL TEMPERATURE?

At home, 8/281 (3%) of the randomly selected babies had a high temperature (rectal temperature >37·9°C) of which only two (25%) were detected by an axillary temperature above 37·2°C (see fig 1A). There were six babies with a high axillary temperature (>37·2°C) of which four (67%) had a high rectal temperature. Therefore, when used at home to detect high temperatures, in this group of babies, axillary temperature had a sensitivity of 25%, a positive predictive value of 33% and a false negative rate of 75%. When used at home to confirm a normal rectal temperature, axillary temperature was very accurate with a specificity of 99%, a negative predictive value of 98%, and a false positive rate of 1%.

In hospital, 93/656 (14%) of the babies had a high temperature by rectal measurement of which 68/93 (73%) were detected by a high axillary temperature (see fig 1B). Of the 99/656 (15%) babies who had a high axillary temperature only 31 (31%) had a high rectal temperature. Therefore, when used in hospital to detect a high temperature, axillary temperature has a sensitivity of 73%, a positive predictive value of 69%, and a false negative rate of 27%. To detect a normal rectal temperature, axillary temperature has a specificity of 94%, a negative predictive value of 96% and a false positive rate of 6%.

EFFECT OF TIME OF DAY ON TEMPERATURE

For the babies seen at home, there was no correlation between rectal or axillary temperature and the time during the day (8 am to 8 pm; for rectal temperature, r=0·008 per hour, SE 0·01, *t*=0·6; for axillary temperature, r=0·02 per hour, SE 0·01, *t*=0·1).

EFFECT OF POSTNATAL AGE ON TEMPERATURE

There was a small positive effect of postnatal age in weeks on rectal temperature ($r=0{\cdot}004$, $SE=0{\cdot}003$, $t=1{\cdot}6$) and a small negative effect on axillary temperature ($r=-0{\cdot}009$ SE $0{\cdot}003$, $t=-2{\cdot}7$) for the babies seen at home.

Discussion

The thermometers used in this study were standard clinical mercury-in-glass thermometers and the nurses taking the temperatures used the technique they use in clinical practice. Although this may have introduced some measurement errors, it means that the accuracy of the temperatures and the conclusions drawn are comparable with those in routine practice.

The normal range for the reference temperatures was taken from a carefully randomised group of babies at home. It is therefore a population reference range rather than a reference based on carefully selected healthy babies. In consequence a small number of babies may have had a fever or been hypothermic. This may have increased the range slightly beyond what is truely normal.

Few other studies have defined the range of daytime rectal and axillary temperatures in normal infants. Wailoo *et al* studied only rectal temperatures of 64 infants at home, mainly at night time, and showed that 90% had a temperature between 36·8 and 37·8°C one hour before bedtime.[6] Those who have compared rectal and axillary temperature have had small numbers of potentially febrile infants and children. In 1984, Kresch compared axillary and rectal temperature in 109 children under 5 years old at a clinic.[4] Fever was defined as a rectal temperature above 38·0°C and an axillary temperature above 37·2°C. He found that for axillary temperature to detect fevers found by rectal temperature the sensitivity was 33%, the false negative rate 67%, and positive predictive value 78%. They concluded, 'Axillary temperature has poor sensitivity, low predictive value and takes eight minutes or longer using mercury-in-glass thermometers. Therefore axillary temperature should not be used in the detection of fever in infants and children'. Ogren, in 1990, used digital electronic thermometers with children in an emergency department.[5] Fever was defined as a rectal temperature above 37·9°C and an axillary temperature above 37·4°C. In 61 rectal/axillary temperature pairs, axillary temperature detected only 17/37 (46%) of the fevers detected rectally. This had a sensitivity of 46% and a false negative rate of 54%. They concluded, 'The present study points out the problem with the axillary temperatures, namely, the high incidence of false negative results. Axillary temperatures may be misleading.' The results and conclusions of these two studies complement the data in this paper that axillary temperature is insensitive.

Temperature was measured at home on babies selected at random, most of whom were well. Temperature would not normally be taken routinely in babies at home. In hospital, temperature measurements are made with the prime purpose of screening for fever; in this situation axillary temperature only had a sensitivity of 73% for detecting those high temperatures which were found by rectal temperature. Therefore, as a screening test for abnormally high temperatures axillary temperature is too insensitive because it will miss a quarter.

It has been suggested that axillary temperature can be used instead of rectal temperature because the two have a significant correlation.[3] A statistically significant correlation between two measurements does not mean that one can be used as a proxy for the other. This study has shown that for a given rectal temperature the range of difference between the two temperatures is too large (up to 3°C) for the mean difference between them (0·7°C) to be a useful value for adjusting axillary temperature to rectal temperature.

Rectal temperature has been banned in some hospitals, and also considered inappropriate for mothers at home because of the possibility of causing rectal perforations.[13] From a review of the literature we suggest that this complication has been over-emphasised and is too rare for rectal temperature measurement to be banned. There have been 20 case reports[14–26] of rectal perforation in infants in the English language literature in the last 30 years which were said to be due to temperature taking. They all occurred in neonates in hospital. The majority of reports only presume the perforation was caused by a thermometer. In only one case was there a history of difficulty taking the temperature.[21] Some cases were almost certainly due to spontaneous perforations, which are well described in all other parts of the bowel.[19 24 27 28] The only case reports of rectal injury from thermometers at home have been due to struggling preschool children and they did not result in perforation.[29]

A recent questionnaire to all members of the British Association of Paediatric Surgeons only revealed two cases of rectal perforation in babies in the first six months of life in the last five years in the UK. Considering that over 700 000 babies are born in this country every year, of which the majority have their rectal temperature taken at least once, the chance of rectal perforation by a thermometer must be less than one in two million. In most other European, Scandinavian, and North American countries rectal temperature is the preferred route for taking babies' temperatures by both professionals and parents (personal communication). Millions of babies must have had their rectal temperatures taken over the years with little reported difficulty. In two trials of mothers using the Baby Check scoring system to grade the illness of babies at home, one of the checks required them to take the baby's rectal temperature with a digital thermometer. Although they only had written instructions on how to take the temperature, only 6% thought it was difficult.[30] Presumably this would be lower if they were taught the technique.

It is important that babies' temperatures should only be taken when clinically indicated. Those doing it should understand that the thermometer should be inserted gently without force and directed at an angle of 30° backwards and not straight into the rectum parallel to the surface of the cot. Modern, plastic, digital thermometers with a liquid crystal display which beeps when the temperature is stable are faster to use than glass thermometers, cannot break in use and are even less likely to cause any damage.

In conclusion, this study has shown that in infants the upper limit of the daytime normal range for rectal temperature is 37·9°C and 37·2°C for axillary temperature. Axillary and rectal temperature measurements can vary by up to 3°C. It is therefore not possible to adjust axillary temperature to rectal by adding the mean difference. If axillary temperature measurements are used to screen for high temperature they will miss a quarter of the febrile babies. This is too imprecise to be used for the accurate recognition of abnormally high temperatures. The chance of causing a perforation by taking an infant's rectal temperature is less than one in two million. If it is necessary to take an infant's temperature the rectal route should be used.

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Streptococcus associated toxic shock

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Abstract

In the past few years, there appears to have been a change in the spectrum of disease caused by group A β-haemolytic streptococcus (GABHS), and a toxic shock-like syndrome caused by this organism has recently been described in adults. We report four children with an acute illness characterised by rapid progression of shock, erythematous rash, multisystem organ involvement, electrolyte derangements, and desquamation who fulfil the previously established diagnostic criteria for toxic shock syndrome. Three of the children had extensive cutaneous and soft tissue infection and the fourth had peritonitis. All four developed bacteraemia. Treatment included aggressive cardiovascular resuscitation and antibiotic therapy. Although no patient died, they suffered multiple and severe complications requiring prolonged treatment and hospitalisation. Streptococcal toxic shock syndrome is a separate and clearly defined entity occurring in previously healthy children.

In 1978, Todd and Fishaut described seven children with an acute disease characterised by fever, mucous membrane hyperaemia, subcutaneous oedema, desquamating erythroderma and rapid progression to hypotension and multisystem organ involvement, and which they called staphylococcal toxic shock syndrome.[1] The disorder subsequently became more widely recognised as an illness affecting young women, which was associated with vaginal colonisation by *Staphylococcus aureus* and the use of tampons.[2] At least 13% of cases are not associated with menstruation but with focal staphylococcal infections and/or colonisation,[3] and a significant proportion of these non-menstrual cases are children.

In the past decade, major advances have occurred in the understanding of the pathogenesis of staphylococcal toxic shock syndrome. It is now well established that most cases are caused by a number of related enterotoxins produced by *S aureus*, the most common of which is the 22 kDa protein called toxic shock syndrome toxin-1 (TSST-1). TSST-1 and other enterotoxins are thought to cause the disorder by activating host inflammatory responses, and in particular by triggering release of cytokines.[4–6]

In the past four years, there have been a number of reports of a toxic shock-like disorder occurring in both adults and children, which has been associated not with *S aureus* but with group A β-haemolytic streptococcus (GABHS).[7–13] Furthermore, there appears to have been an increase in the prevalence of serious invasive disease due to GABHS in many parts of the world.[14–26]

In order to illustrate the clinical and pathological features of the disease, we report four children with streptococcus associated toxic shock syndrome and discuss the mechanisms involved in its pathogenesis.

Patients and methods

Streptococcus associated toxic shock syndrome was diagnosed in four children between February 1988 and November 1990. Three were admitted to the Hospital for Sick Children, Great Ormond Street, London, and one to Guy's Hospital, London (table 1). All four cases fulfilled the diagnostic criteria for staphylococcal toxic shock syndrome,[27] but in each case GABHS was isolated from the blood (table 2).

Table 2 Criteria of staphylococcal toxic shock syndrome (TSS) in four children with streptococcus associated toxic shock syndrome

	Case No			
	1	*2*	*3*	*4*
Staphylococcal TSS criteria				
Temperature >38·9°C	+	+	+	+
Rash	+	+	+	+
Desquamation	+	+	+	+
Hypotension	+	+	+	+
Multisystem involvement				
Gastrointestinal	−	−	+	−
Muscular	+	+	−	−
Mucous membrane	+	+	−	+
Renal	+	−	−	−
Haematological	−	+	+	−
Hepatic	+	+	−	−
Central nervous system	−	+	−	+

+, Present; −, absent.

Table 1 Clinical characteristics of four children with streptococcus associated toxic shock syndrome

Case No	*Age*	*Sex*	*Clinical presentation*	*Initial symptoms*	*Prodromal period**	*GABHS isolation*
1	10 years	F	Shock, fasciitis	Fever, rash	6 days	Blood, skin wound
2	22 months	F	Shock, cellulitis	Fever, focal swelling	12 hours	Blood, bullae, nose, skin
3	13 days	F	Peritonitis, shock	Diarrhoea, rash	3 days	Blood, nose, peritoneal fluid
4	10 weeks	F	Shock, cellulitis	Fever, focal swelling	18 hours	Blood

*From onset of symptoms to shock.
GABHS, Group A β haemolytic streptococci.

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Microorganisms were recovered and identified according to standard procedures.[28] Antibiotic susceptibility was determined by the disc diffusion method in the microbiological laboratories of the respective hospitals.

CASE REPORTS

Case 1

A previously healthy 10 year old girl experienced pain and swelling over both ankles three days after sustaining a cut below her left knee. She subsequently developed a non-specific macular erythematous rash and fever and was admitted to a local hospital. During the ensuing five days, she became increasingly tachycardic and jaundiced, and blistering areas were noted in the right upper limb.

After 24 hours of progressive drowsiness and hypotension she was transferred to Guy's Hospital where, on arrival, she was toxic and lethargic but responsive. Her temperature was 39°C, heart rate 150 beats/min, respiratory rate 40/min, and systolic blood pressure 85 mm Hg. She had red lips and tongue with conjunctival hyperaemia and mild icterus. A soft 2/6 systolic murmur was noted. The liver was 2 cm below the right costal margin. Her ankles and wrists were intensely swollen. A fine papular generalised rash with desquamation, particularly over the trunk and limbs, was found in conjunction with large yellow blisters and necrotic areas over her right forearm and lateral aspect of her left foot. The pulse in the right radial artery was absent, though detectable on Doppler examination. Initial investigations were as follows: haemoglobin concentration 87 g/l, white cell count 30×10^9/l with 25×10^9 neutrophils, platelet count 251×10^9/l, and erythrocyte sedimentation rate 45 mm/hour. Biochemical findings showed concentrations of sodium 125 mmol/l, urea 22·4 mmol/l, creatinine 175 μmol/l, bilirubin 71 mmol/l and albumin 31 g/l, creatine phosphokinase 3108 U/l and aspartate aminotransferase 181 U/l. Urine contained granular casts and blood cells, and was positive for myoglobin and protein (3+), urinary sodium was less than 10 mmol/l. Blood cultures and swabs from the cut below the left knee grew GABHS.

She was resuscitated with large volumes of colloid and required inotropic support with dobutamine and dopamine. Despite an adequate central venous pressure, she remained poorly perfused; a continuous infusion of prostacyclin was introduced as a vasodilator. She was electively ventilated and required full sedation and paralysis. High dose penicillin and flucloxacillin were started. Her oxygen requirement increased over the next few hours and radiological changes consistent with adult respiratory distress syndrome appeared. After resuscitation, her renal and hepatic function returned slowly to normal.

Swelling of the soft tissues over her right wrist and elbow joints became more noticeable. As she was weaned off muscle relaxant drugs, a compartment compression syndrome was diagnosed in her right forearm and in both legs. Fasciotomy was carried out in all affected limbs and yellow fluid drained from the fasciae. In spite of the decompression of her forearm, the muscles looked progressively less viable over the next few days. A bone scan suggested an avascular right ulna. Antibiotic therapy was changed to cefotaxime and clindamycin. Sensation of the right hand disappeared, and three weeks after admission, amputation of the right upper limb below the elbow was carried out. Additional amputation of her feet was avoided, although extensive skin grafting was necessary. Progressive clinical recovery followed with re-establishment of normal renal, hepatic, and pulmonary function. She returned to the local hospital five weeks after initial admission.

Case 2

A 22 month old girl presented to a local hospital with a one week history of cough, fever, and mild facial swelling. One day before admission, she developed multiple red bullae over her trunk and limbs. On admission, she was febrile (40·6°C), with a rate of 200 beats/min, and blood pressure of 65/40 mm Hg. She had generalised subcutaneous oedema and delayed peripheral perfusion. A presumptive diagnosis of septic shock was made and aggressive fluid resuscitation (in excess of 300 ml/kg) was instituted. Initial antimicrobial therapy included flucloxacillin, fusidic acid and gentamicin. Laboratory investigations recorded haemoglobin concentration 82 g/l, white cell count $3\cdot5\times10^9$/l, neutrophils $1\cdot9\times10^9$/l, platelet count 90×10^9/l, concentrations of sodium 129 mmol/l, potassium 2·7 mmol/l, calcium 1·86 mmol/l, creatinine 48 μmol/l, urea 7·1 mmol/l, albumin 22 g/l, fibrinogen 4·6 g/l and fibrin degradation products >20 μg/ml, prothrombin time 51 seconds (control 14 second), partial thromboplastin time 35 seconds (control 32 seconds), aspartate aminotransferase 152 U/l and creatine phosphokinase 221 U/l. GABHS was grown from blood, fluid from bullae, and her nose. Penicillin was added to her antimicrobial therapy.

After resuscitation her condition improved but she continued to be febrile and developed swelling over her left forearm and calf. She was referred to the Hospital for Sick Children with a possible diagnosis of necrotising fasciitis. On arrival she was febrile (39°C) with a heart rate of 190 beats/min. She had enlarged and tender lymph nodes in the left cervical chain and generalised subcutaneous oedema. A left sided cervical mass anterior to the carotid vessels was demonstrated on cervical ultrasound and thoracic computed tomography. A technetium white cell scan suggested an inflammatory lymphadenitis as there was marked focal uptake of the labelled white cells. A nuclear magnetic resonance scan revealed multifocal soft tissue lesions in the left side of the neck and extending into the superior mediastinum. Surgical exploration was carried out, and necrotic tissue was obtained, but there was no evidence of pus formation. Histologically, necrotic and infarcted tissue was seen which contained Gram positive cocci in chains. No growth in culture was observed. Gentamicin was discontinued and rifampicin commenced.

Extensive desquamation became apparent by day 8 after admission. After surgery, the child started to improve and the fever abated although she developed severe hypokalaemia (potassium concentration 1·4 mmol/l) which responded to treatment. She was discharged two weeks later. Extensive virological and bacteriological tests failed to show any other pathogen. There was progressive clinical and radiological resolution of the cervical mass over the next six weeks.

Immunological investigations showed normal total immunoglobulins, Nitroblue tetrazolium reduction and lymphocyte responses and subsets, but low IgG_1 and IgG_2 values were demonstrated on initial investigation. On repeat studies four months later all immune function tests were normal.

Case 3

A 13 day old girl was referred to the surgical unit at the Hospital for Sick Children, London, with a three day history of erythematous rash and diarrhoea, vomiting for 24 hours, and refusal to feed. On admission, examination showed she had a toxic appearance, central cyanosis, and poor peripheral perfusion. Her blood pressure was 54/30 mm Hg, heart rate 160 beats/min, and central temperature 39·2°C with a gap between central and peripheral temperature of 3·6°C. Her abdomen was grossly distended and rigid, and the bowel sounds were absent. The rash had become confluent and spread to her back. Initial investigations recorded haemoglobin concentration 108 g/l, white cell count $23{\cdot}5\times10^9$/l with 93% neutrophils, platelets 92×10^9/l, concentrations of sodium 125 mmol/l, potassium 3·3 mmol/l, creatinine 53 μmol/l, urea 9·3 mmol/l, calcium 2·1 mmol/l, and albumin 24 g/l, prothrombin time 39 seconds (control 10–14 seconds) and partial thromboplastin time more than 120 seconds. Abdominal radiographs showed considerable bowel distension and evidence of free fluid.

Over the next 18 hours she became profoundly shocked and required over 300 ml/kg of plasma and crystalloids in the first 18 hours to maintain perfusion, blood pressure, and urine output. A laparotomy was performed because a surgical cause of the shock and the abdominal findings could not be excluded. Purulent peritoneal fluid was found but no other pathology. Microscopic examination contained 4500 white blood cells/l, protein 10 g/l, and abundant Gram positive cocci. High dose penicillin was administered. Blood and peritoneal cultures grew GABHS sensitive to penicillin.

After the operation she required mechanical ventilation for three days. Two days later she began to desquamate and this continued for more than one week, affecting most of her body. Over the next 10 days she continued to have a spiking fever (39–39·5°C), associated with leucocytosis and neutrophilia. Chest radiographs showed patchy consolidation in the right lower lobe. Subsequently, her clinical condition improved, and her renal function, electrolyte values, and platelet count slowly returned to normal. The patient was finally discharged after 22 days in hospital having discontinued antibiotic therapy the day before. She continued having intermittent fevers for a further 20 days. On follow up one and four months later she was found to be asymptomatic and thriving.

Case 4

Pallor and hypothermia developed in a 10 week old girl. Over the next 18 hours a small red lesion in the left submandibular region became indurated, swollen, and hot, and extended to involve both sides of her neck. On admission to the Hospital for Sick Children she was febrile (39·5°C), her blood pressure was 75/35 mmHg, heart rate 200 beats/min, and respiratory rate 65/min. The oral mucosae were reddened and she was very poorly perfused. She was resuscitated with plasma and crystalloids, requiring 350 ml/kg in the first day. In addition, she was started on flucloxacillin, gentamicin, and ampicillin. Two hours after admission she developed metabolic acidosis, bradycardia, and apnoea, requiring mechanical ventilation. On her initial investigations she was found to have a haemoglobin concentration of 80 g/l, sodium 123 mmol/l, potassium 2·4 mmol/l, chloride 93 mmol/l, calcium 1·9 mmol/l, high of creatine phosphokinase at 826 U/l, and prolonged coagulation tests. Two right sided focal seizures were observed in the first 6 hours. Cerebrospinal fluid examination was normal. Blood cultures grew GABHS, and penicillin plus gentamicin were continued. Within the first two days, she developed progressive anaemia (lowest haemoglobin 70 g/l) requiring packed red blood cells, and a generalised erythematous rash which later desquamated. Over the next 48 hours, her shock resolved but she continued to require ventilation. Mechanical ventilation was stopped after three days. The cellulitis subsided slowly and the patient was discharged on oral antibiotics on day 14.

Discussion

The four children reported in this series all suffered from a fulminant disorder characterised by shock, multisystem involvement, and a distinctive erythematous rash, which fulfilled the diagnostic criteria for toxic shock syndrome, but was associated not with staphylococcal infection but with GABHS sepsis. These cases are strikingly similar to the reports of streptococcal toxic shock syndrome in adults,[7–11] and to a similar disorder previously described after varicella infection in three children.[12 13]

The clinical and laboratory features in these cases are sufficiently distinctive and dramatic that they could hardly have gone unrecognised by clinicians in the past few decades. The question therefore arises as to whether the growing number of reports of streptococcal toxic shock syndrome represents the emergence of a 'new' streptococcus associated syndrome, or whether it reflects the rediscovery of an entity which may have been more common in the preantibiotic era.

Before 1940, streptococcal infections accounted for a major proportion of infectious conditions seen in many centres in developed countries. Deaths from streptococcal bacteraemia, severe scarlet fever, and erysipelas were common.[10 21] The fatality rate for streptococcal bacteraemia was found to be 72% in the total population and 62% in children under 15 years old in 1937.[29] Based on the clinical description of the disease in those patients, it is possible that the disorder now termed streptococcal toxic shock syndrome accounted for some of the severe cases and deaths. With the decline in the incidence of streptococcal infections in the developed world, modern clinicians may have simply lost their familiarity with this particular complication. However, a definite increase in the incidence of serious disease associated with GABHS has been noted in the past decade. Reports describing severe generalised and focal infections in children with and without underlying disorders have appeared.[15–26] In addition, there is evidence that non-suppurative complications of streptococcal infection, such as rheumatic fever, have re-emerged in scattered areas in the United States.[30 31] Increased prevalence of pathogenic strains of GABHS has been suggested as the explanation for the rising number of cases of severe infection.[32]

The pathogenic mechanisms by which the streptococcal toxic shock syndrome is caused are unknown, but it is likely that the production of one or more toxins induces the clinical manifestations of the disease. GABHS has the capability to produce at least four serologically different types of exotoxins.[33 34] All of them are pyrogenic, may enhance host susceptibility to lethal endotoxic shock, produce non-specific stimulation of T lymphocyte proliferation, enhance delayed hypersensitivity, and suppress immunoglobulin synthesis.[34] In addition, they may act as potent release inducers of tumour necrosis factor.[6] In view of the clinical similarities of the staphylococcal toxic shock syndrome to the syndrome seen in our patients, it is of interest that there seems to be considerable amino acid homology between and A and C streptococcal toxins and staphylococcal enterotoxins.[35] These toxins not only have a similar structure but also common modes of action on the immune system. TSST-1 and other staphylococcal enterotoxins, streptococcal pyrogenic exotoxins, and some mycoplasma toxins act as superantigens, binding to specific variable β chain regions of the T cell receptor in association with human class II major histocompatibility complex proteins, and stimulating T cell proliferation and cytokine release by the T cells.[35 36] Release of these inflammatory mediators probably accounts for the clinical manifestations of both the staphylococcal and streptococcal associated diseases.

Despite the clinical similarities and the common mode of action of their related toxins, there are a number of clinical differences between the streptococcal and the staphylococcal syndromes. In staphylococcal toxic shock the site of staphylococcal infection is often a trivial focus or asymptomatic colonisation, and bacteraemia seldom occurs. In contrast, most cases of streptococcal toxic shock syndrome are associated with severe streptococcal focal infection and bacteraemia. Desquamation is less frequently seen in the streptococcal syndrome. Among 26 adults only eight (31%) had desquamation.[8 9] In view of the extensive soft tissue involvement in streptococcal toxic shock, surgical intervention is more commonly required than in the staphylococcal syndrome. Finally, the timing of events may differ from that in the staphylococcal syndrome as the rash in the streptococcal syndrome may appear late in the disease and coexist with the desquamation.

From the therapeutic point of view, prompt recognition and understanding of the natural history and progression of the disease should lead to an aggressive intensive care approach. Correction of hypovolaemia by infusion of large amounts of colloid, inotropic support, and if necessary ventilatory assistance must be implemented to correct shock and restore adequate oxygen delivery to the tissues. In addition, prompt antimicrobial therapy should be started, and penicillin remains the drug of choice for GABHS infections. Until the microbial cause has been identified, antistaphylococcal cover should be included. Surgical intervention to remove focal infection and reduce the amount of toxin released may be necessary. Despite the fulminant nature of the illness and the prolonged and complicated course, complete recovery is possible with early and aggressive treatment.

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Implantable intravenous access device

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Abstract

The use of a fully implantable device for venous access is described in two infants with transfusion dependent haemolytic anaemia. This device is a possible improvement in the treatment of infants needing long term venous access, although doctors should be aware of the infrequent complications.

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An infant with pyruvate kinase deficiency, who required repeated blood sampling and was dependent upon monthly transfusions, presented problems with venous access and became greatly distressed by hospital visits. We decided to employ a means of permanent intravenous access and thought that a fully implantable device would be the correct choice to preserve her otherwise normal and healthy lifestyle. The Infuse-a-port (Novamedix) or Implantofix (Braun), represent small and lighter modifications of the original Port-a-cath (Pharmacia Deltec) so was the appropriate choice. After successful use in this patient the implantable device was chosen for use in a second case as described below.

Case reports

CASE 1

After a normal pregnancy and delivery a mother noted her baby girl to be jaundiced at 8 hours of age. Investigations confirmed haemolysis. The baby required weekly transfusions to maintain a haemoglobin concentration above 90 g/l. A diagnosis of pyruvate kinase deficiency was made at 3 months of age. Blood sampling by finger prick or venous sampling and venous cannulation was performed for several months with increasing difficulty and distress. The Implantofix catheter and port system was sited and has been used successfully and without complication for over two years.

Figure shows the use of the Implantofix. Sterile procedure is mandatory, and the Huber point, non-coring 'Gripper' needle (Pharmacia Deltec) is being used here to take blood before transfusion. The needle must subsequently be immobilised to prevent dislodgement.

CASE 2

A boy presented at 3 months of age with pallor. Investigations confirmed haemolysis. A diagnosis of recessive spherocytosis was made and while being investigated peripheral venous access for transfusion was impossible and an indwelling, external-internal Broviac-type central line was inserted.

Unfortunately the fastidious cleanliness required, even with assistant domiciliary care and advice, was not easy in this chubby, healthy baby and the line was complicated by infection within three months.

In view of the previous success of the Implantofix we removed the infected catheter and three weeks later, when the infection had resolved, an Implantofix was successfully inserted.

Methods

The surgical procedure for insertion has been described in detail by Kondi *et al.*[1] The only difference between their procedure and ours was that we used general anaesthesia. Venous access can be gained via the external jugular, internal jugular, cephalic, facial, subclavian, axillary, saphenous or femoral veins for passage of the catheter. The catheter should be already trimmed to the appropriate length and the distal end is then burrowed subcutaneously and fixed to the port which is buried in a subcutaneous pocket. This is usually sited over the chest wall, providing easy access and a firm backing to the port. The position of the catheter is checked by fluoroscopy (or radiography if this facility is not available) at the time of surgery.

The port is accessed immediately and an infusion maintained for 24 hours; this is a routine that we use to be satisfied of free flow. Three intravenous doses of vancomycin 22 mg/kg at intervals of 12 hours are given to avoid perioperative contamination, the first being initiated in the operating theatre. At completion of the infusion the device is 'heparin locked' with injection of 5 ml heparin, 100 U/ml. The weaker strengths of heparin are not sufficient to maintain the anticoagulant effect.

Scrupulous attention to the wounds is given to prevent risk of infection. Heparin locking is performed at weekly intervals for the first month, at least monthly therafter, and after each sampling or transfusion.

In both babies the device was inserted without complication. The wounds healed well and there have been no infection related or other problems for a patient total of four years. Both children require top-up transfusions at intervals of four to six weeks to maintain adequate haemoglobin concentrations. These and any needle accessing must be performed using the special Huber point, non-coring needles (see figure). As the life of the silicon membrane of the port is said to be 2000 punctures, some years of use can be anticipated. We perform radiography every four months to observe the position and condition of the systems as the children grow.

Discussion

The length of use of the subcutaneous systems, combined with the lack of restriction on lifestyle in otherwise healthy infants, allows their increasing use with great clinical advantage.[2] Risk of infection is widely reported to be lower for the implanted devices than the subcutaneous tunnelled internal-external lines.[3] We suggest that this applies particularly in infancy. Likewise thrombotic occlusion is less frequent[4] and there is no risk of external fracture. Internal fracture can be anticipated by chest radiography and looking for the 'pinch-off' sign—that is, narrowing of the catheter at any point (usually between clavicle and first rib). If a catheter fragment should embolise it can be safely retrieved using cardiac catheterisation.

Blockage of the catheter can be treated with urokinase, and persistent withdrawal occlusion has also been shown to resolve with thrombolytic treatment when secondary to fibrin sheath formation on the catheter tip.[5 6] If the catheter and port should separate, surgical remedy is usually required.

The lack of disruption of normal daily activities after successful implantation is of special importance in children. We have noticed that family stresses are relieved; that is an important aspect of patient care. There is no percutaneous entry site requiring special care or dressing and the child can bathe once the wound has healed. Visits to the hospital are less of a strain because venous access is more readily assured. The onus on medical staff to obtain peripheral venous access in these chubby and otherwise extremely healthy infants is alleviated. Other reports also comment specifically on patient and parent approval and acceptance of these subcutaneous devices.[4]

Provided the physician is aware of the infrequent complications, we hold that insertion of implantable intravenous access devices in infants, who present long term problems, greatly enhances medical care provided for the baby and family. Further experience will show whether these systems provide complication-free access in our patients until they are old enough for elective splenectomy to be considered. Experience thus far suggests that this is a safe and happy way to achieve long term intravenous access to assist in optimal management and promote normal development in growing babies.

We thank Professor L Luzatto for helpful advice at diagnosis, Dr G P Taylor for permission to describe patients under his care, and Mr C M Vickery for his surgical expertise.

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Paediatric psychotherapy: a service in a general outpatient clinic

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Abstract

The service of paediatric psychotherapy to a general paediatric outpatient clinic is described. Using techniques developed to suit paediatric patients a median of nine patients each clinic were treated. Referral symptoms resolved in a median time of four months after a median of seven sessions. This model for the management of paediatric patients with emotional and behavioural difficulties may allow an effective and efficient use of psychotherapy time.

Emotional and behaviour difficulties in children account for a large proportion of the problems seen in paediatric clinics, 28% in a recent report.[1] After referral, further help may be sought from a child psychiatrist, psychotherapist, clinical psychologist, or social worker, often at another location such as the child guidance clinic and inevitably with further delay. Poor integration of paediatric and psychiatric services and difficulties in communication between them have been highlighted.[2] It would appear then that a service delivered directly to a general clinic could have many advantages. The benefits of liaison child psychiatry and psychotherapy and its multidisciplinary team approach to specialist paediatric units have been well described elsewhere.[3–5]

This report describes a paediatric psychotherapy service delivered directly to a general paediatric outpatient clinic. This complements the existing child guidance and child psychiatric services to hospital and community. The goal was to discover if it was possible to deliver an effective and efficient service in terms of improvement in referral symptoms and throughput.

Methods

Children were referred from general practitioners, house staff, nurses, and health visitors. The waiting space was shared with two adult clinics. The clinic ran from approximately 1 pm until 6 pm to allow attendance outside school hours if appropriate, to accommodate varying consultation times, and to allow a throughput which would facilitate frequent visits and thus keep up the momentum of treatment.

A consultant paediatrician supervised the management of any physical disorders which existed. When no organic disease was identified, the child and family were reassured. During both appraisal and treatment the paediatrician used, where appropriate, behavioural techniques such as the preparation of star charts, diaries, and task direction for the establishment of routines such as bedtime and mealtimes.

When it was felt that the emotional complexities of a child's or family's difficulties were such that behavioural techniques were not appropriate or needed complementing, the family was prepared for referral to the psychotherapist, who worked in a neighbouring room. An introduction was made during the same meeting and an appointment given, usually for the next week. Thereafter children with both physical and emotional components to their symptoms, for example, soiling, made one visit for two appointments.

The psychotherapist's methods are discussed elsewhere[6] but in summary involved working with the child individually as well as with his/her family. The approach did not use tests or questionnaires but relied on what the child and family communicated through play, talking, silence, expression of feelings—especially anger—and the relationship that developed between therapist and child and family. Early on families may have been asked to prepare a 'concern' diary. This involved the parents noting down each day, on average for a fortnight, everything that concerned them in relation to the child, for example, the events leading up to and around undesirable behaviour. This served a number of purposes, for example, to see if there was a pattern of anxiety that manifested itself in maladaptive ways and to encourage a feeling of active parental involvement.

Referrals in 1988–90

Reason for referral	*Referrals to paediatrician*	*Referrals from paediatrician to psychotherapist*
Soiling	63	14
Sleep disturbance	32	1
Eating disorders	27	8
Abdominal pain	24	6
Eneuresis	26	4
Conduct disturbance	25	23
Headaches	13	4
Bereavement (excluding SIDS and perinatal death)*	14	4
Other†	45	30
Total	269	94

*SIDS=sudden infant death syndrome.
†Includes anxiety, chronic illness, adolescent difficulties, non-compliance with drug treatments.

Each child was seen invidually, usually once a week or once every two weeks, for 20–35 minutes each time. As the need arose the meetings also included the parents and siblings or the parents on their own. Children with life threatening illnesses such as anorexia nervosa, severe depression, autism, or who needed complex family systems work, were referred to complementary services. Consultations and visits to schools and liaison with social services were undertaken as necessary.

Results

Between 1988 and 1990, 269 children with difficulties which may have had either emotional or behavioural contributing factors were referred to the consultant paediatrician. The table shows that the pattern of referral symptoms to the paediatrician was different from that of the paediatrician to the psychotherapist suggesting that the more task oriented behavioural approach of the paediatrician was successful in the treatment of some problems, for example, sleep disturbance, than others, for example, conduct disturbance. Fourteen referrals from other sources made a total of 108 to the psychotherapist. Thirteen did not attend after the first introduction, nine dropped out of treatment, 18 continued into 1991, and three returned after discharge. Thus 68 completed treatment. Fifty seven were discharged with referral symptoms resolved, four discharged without improvement, and seven were referred elsewhere.

There were 83 clinics and the median number of patients/clinic was nine (range 3–13) and the median age was eight years (range 1–17). The median length of completed treatment was four months (range 1–24). The median number of sessions per patient was seven (range 1–72). Five patients were in treatment for two to three years.

Discussion

One advantage of a parallel service is that families attend only one clinic where they have two appointments. Waiting time for an appointment with any of the child psychological services is eliminated. The setting may be less threatening for both the uptake and carrying through of treatment. The waiting area accommodates adults and children for other clinics. Perhaps this allows the psychotherapist to be seen as part of a team and removes some of the mystique and stigma often associated with referral for treatment of emotional or behavioural problems.

A very reasonable criticism of psychotherapy is that treatment is frequent and lengthy. The experience in the clinic suggests that there are a number of children who may benefit from short term treatment, thus making it available to more children. Psychotherapy does not lend itself easily to clinical trials. It would be difficult to compare this model with other approaches to discover whether it is as effective in terms of throughput and outcome. The only outcome described here is the resolution of referral symptoms at the time of discharge and we recognise that this has not been evaluated objectively. Nevertheless this parallel service would seem to address some of the problems of referring children with emotional and behaviour problems for help.[2] The experience has also been of educational value, not only in the development of short term psychotherapeutic techniques,[6] but also in the training of medical staff in the different ways to listen to how children and families communicate their concerns and the ways in which to work with them.

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Coeliac disease and lymphangiectasia

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Abstract

Two out of 74 children with coeliac disease demonstrated severe intestinal protein loss. In both children a serial small bowel biopsy specimen showed intestinal lymphangiectasia to be also present. Intestinal lymphangiectasia is another disorder that may be associated with coeliac disease.

Several disorders have been found to occur in association with coeliac disease. Cystic fibrosis, ulcerative colitis, Crohn's disease, collagenous colitis, giardiasis, and recurrent oral and small intestinal ulceration have all been reported in children and adults with coeliac disease.[1 2] However, the coexistence of coeliac disease with intestinal lymphangiectasia has not so far been described. Both diseases may present with substantial enteric protein loss and steatorrhoea and potentially mimic each other, although the distinctive small intestinal mucosal changes will discriminate between the two.

We describe for the first time coeliac disease and intestinal lymphangiectasia occurring together in two children with severe enteric protein loss.

Patients and methods

Between May 1981 and December 1985, 74 children were diagnosed as having coeliac disease according to the criteria of the European Society of Paediatric Gastroenterology and Nutrition.[3] In addition to chronic diarrhoea, failure to thrive, and steatorrhoea two of the children also had clinical and laboratory evidence of severe intestinal protein loss (table).[4] Case 1 also developed the clinical features of tuberous sclerosis: fibroangiomatous naevi, adenoma sebaceum, and brain tubers on computed tomography at the age of 7·5 years.

In both children small intestinal mucosal biopsy specimens demonstrated either total or subtotal villous atrophy with other microscopic features commonly seen in coeliac disease: crypt hyperplasia, increased number of intraepithelial lymphocytes, heavy lymphoplasmocytic infiltration of the lamina propria, and appreciable lymphangiectasia (fig 1A and 2A). Sweat chloride concentration, stool chromatography for sugars, duodenal juice and stool microscopy for parasites, liver function tests, urinalysis, and chest radiography were all normal or negative. Concentration of coagulation factors II and VII were decreased and returned to normal after parenteral administration of vitamin K. Both children initially demonstrated a complete absence of serum IgA and IgM. Case 1 had a low IgG concentration of 1·9 g/l (normal range 7·62 (2·09) g/l). Case 2 also had a decreased IgG concentration of 1·6 g/l (normal range 6·61 (2·19) g/l). Examination of peripheral

Details of the two patients with coeliac disease and lymphangiectasia

Case No	*Sex*	*Age (months)*	*Oedema*	*Serum albumin (g/l)*	*Faecal fat* (g/100 g stool)*
1	F	25	Generalised	10	68·4
2	M	12	Legs and eyelids	18	55·8

*Three day collection.[4]

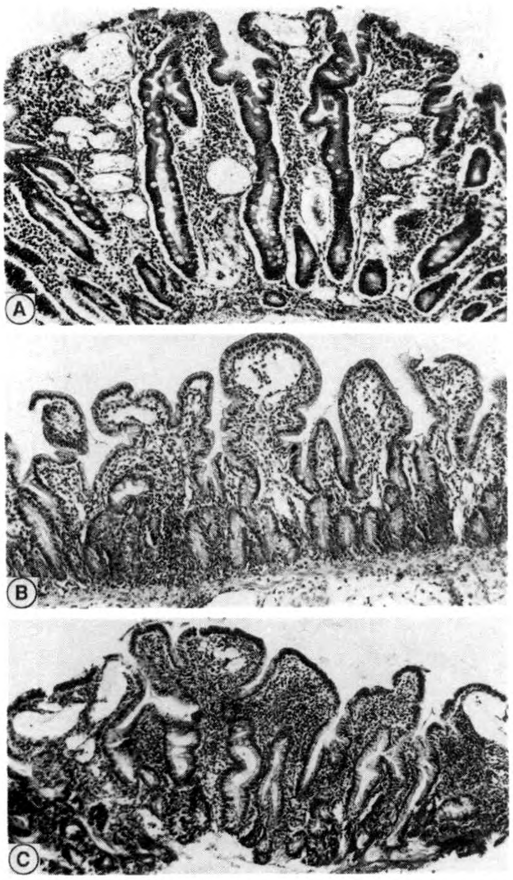

Figure 1 Case 1: (A) Initial biopsy specimen demonstrating subtotal villous atrophy, crypt hyperplasia, and dilated lymphatics in the lamina propria. (B) Specimen taken after restoration of the villous architecture to normal after gluten free diet. Dilated lymphatics are also present. (C) Specimen taken after gluten challenge showing shortened and blunted villi and hyperplastic crypts. Lymphangiectasia persists. (All haematoxylin and eosin stain×100.)

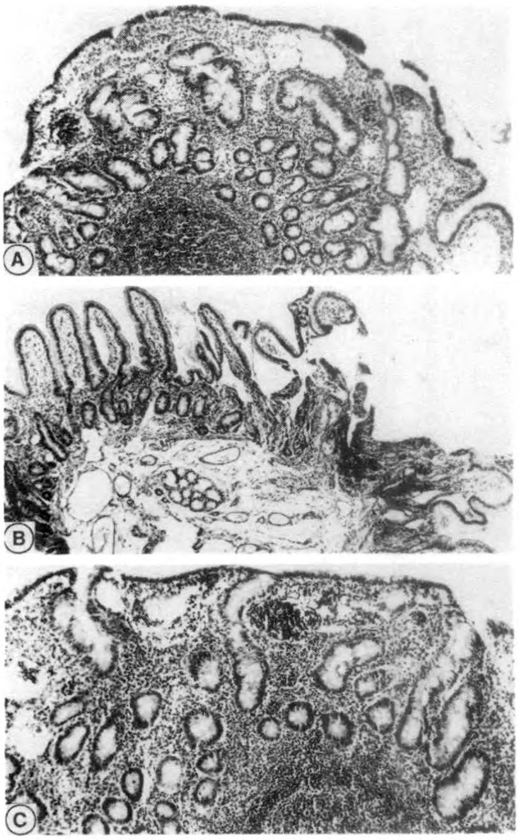

Figure 2 Case 2: (A) Initial biopsy specimen demonstrating subtotal villous atrophy and cystically dilated lymphatics. (B) Specimen taken after gluten free diet showing that villous architecture has returned almost to normal. Lymphangiectasia still present. (C) Specimen taken after gluten challenge showing evident total villous atrophy and lymphangiectasia. (Haematoxylin and eosin stain in (A) and (C) ×100, in (B) ×50.)

blood T lymphocytes from case 2 (E rosette test) showed decreased values of 30·5 (normal range 60–80%).

A gluten free, low milk, low fat, high protein diet with vitamin supplementation led to a gradual improvement during the next eight months in both patients. Diarrhoea ceased and they both reached an appropriate weight and height. Serum albumin and immunoglobulin concentrations returned to normal.

After two years on a gluten free diet both children underwent gluten challenges after confirmation of histological remission. Histologically relapse occurred in each child after three months on gluten (fig 1B, 1C and 2B, 2C). Small bowel biopsy specimens taken at follow up demonstrated the persistence of lymphangiectasia.

During a six year follow up, case 1 remained on a strict gluten free diet, but on several occasions ate large amounts of fatty foods. Her stools became voluminous and pale and her eyelids and legs swollen. At the time of her first relapse, at the age of 3·5 years, her serum albumin concentration decreased to 20 g/l, IgG to 2·6 g/l, and IgM to 0·17 g/l.

During 2·5 years of follow up, case 3 has not relapsed clinically, has remained strictly on the recommended diet, and thrived.

Discussion

Severe intestinal protein loss and steatorrhoea are distinct features of a variety of gastrointestinal disorders including coeliac disease and intestinal lymphangiectasia.[5] Clinically, both diseases may present with chronic diarrhoea, failure to thrive, and oedema and thereby mimic one another.[6] Moreover, appreciable hypoproteinaemia, steatorrhoea, hypocalcaemia, and abnormal laboratory indices of intestinal protein loss, for example raised faecal α_1-antitrypsin clearance, may occur in both coeliac disease and intestinal lymphangiectasia. The distinctive small intestinal mucosal changes and the presence of lymphopenia, hypoimmunoglobulinaemia, and T cell depletion are helpful in differentiating intestinal lymphangiectasia from coeliac disease. Sometimes the normal villous architecture of the jejunal villi may be distorted appreciably by large dilated lacteals in intestinal lymphangiectasia, causing appearance of villous atrophy.

Our patients suggest an association between intestinal lymphangiectasia and coeliac disease. The severe intestinal protein and fat losses, with associated mineral and vitamin deficiencies, which characterise intestinal lymphangiectasia may considerably exaggerate both the presentation and the course of coeliac disease. If not recognised promptly, intestinal lymphangiectasia may thereby cause treatment failure in children with coeliac disease. Multiple small intestinal biopsy specimens, perhaps taken endoscopically, may be helpful in establishing the presence of intestinal lymphangiectasia in children with coeliac disease.[3 6] As intestinal lymphangiectasia may be an incidental finding, additional data, for example the presence of hypoimmunoglobulinaemia and T cell depletion, may help in determining the clinical significance of lymphangiectatic mucosal changes.[5 6] These patients with coeliac disease need lifelong diet management.

The authors thank Dr Ian W Booth for his contribution to this manuscript.

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Positive end expiratory pressure via a portable system in thoracic dystrophy

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Abstract
The provision of positive end expiratory pressure, via a unique portable system, in the long term management of a child with thoracic dystrophy is reported. The system uses low gas flow enabling a reduction in equipment and simplification of the circuit as compared with a standard continuous positive airways pressure system.

For a child requiring long term continuous positive airways pressure (CPAP), we devised a system for providing positive end expiratory pressure (PEEP) using low flows of oxygen. The system, initially employed to provide CPAP, was a standard high flow Bennett system necessitating that the patient be restricted to his cot on the infants' ward where there are piped supplies of oxygen and air. In order for him to become mobile around the hospital and ultimately at home, we devised a portable PEEP system.

Description of the system
Our system (figure) employed the same CPAP valve and T piece as the high flow pipeline system but required a mixer with a non-return valve to allow the use of low flow oxygen without loss of the PEEP from the valve and to prevent rebreathing. The system consisted of a T piece with an oxygen connector (A) in series with a 1950 non-return valve (B) on one limb, and the CPAP valve (C) on the other limb, the assembly being connected to the infant by a standard 15 mm Portex connector.

The inspired oxygen delivered by the system depends upon the flow of oxygen into the circuit, the respiratory rate, and the inspiratory flow rate of the patient. An increase in the respiratory rate will reduce the time available for oxygen to accumulate in the wide bore tubing during expiration and therefore reduce the fractional inspired oxygen ($\mathrm{FIO_2}$). An increase in inspiratory flow will increase the volume of room air entrained via the 1950 one way valve reducing the $\mathrm{FIO_2}$. Therefore, the oxygen tension in the circuit cannot be accurately predicted from the present oxygen flow; however, we have found that a flow of 500 ml/min delivers approximately 28% oxygen to our patient. Increasing the flow of oxygen to the circuit up to 1 l/min increases the $\mathrm{FIO_2}$ to 36%, and 2 l/min to 48%. Rebreathing is prevented by the presence of the 1950 one way valve and also by the one way valve in the CPAP valve. As flow in the circuit is generated by the child's inspiratory effort the system provides PEEP, not CPAP.

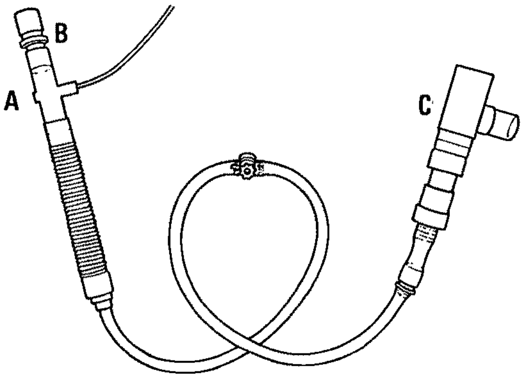

Diagram of system described.

Case report
Soon after birth our patient, now aged 18 months, was noted to have a number of dysmorphic features including the Pierre Robin syndrome (cleft of the soft palate, micrognathia, and glossoptossis), macrocephaly, severe hyphoscoliosis, a small thorax, a penile web attached to the scrotum, and generalised hypotonia.

Investigations were carried out to evaluate his dysmorphology. His chest radiograph showed short flat ribs with a bell shaped thorax, but no posterior rib defects. Lung function tests at 5 months of age confirmed small volume lungs (total gas volume 25 ml/kg) with a restrictive pattern and a small component of airways obstruction (airway resistance 39·6 to 51 cm H_2O/l/sec). Serial chest radiographs from 3 months to the present have shown little chest growth, with significant atelectasis present at most times. Skeletal survey showed no abnormality of the skull, long bones, or pelvis. These investigations confirm our clinical impression of a thoracic dystrophy, and our search continues in order to define the underlying syndrome.

From birth our patient had respiratory difficulties with persistent tachypnoea and recession and recurrent episodes of pneumonia. At 9 months, respiratory failure ensued necessitating assisted ventilation. A tracheotomy was performed on day 8 as attempts at extubation had failed due to upper airway compromise. He was weaned on to CPAP (5 cm) on day 14, requiring 30% oxygen via a tracheostomy mask to maintain oxygen saturations above 92%. Soon after the CPAP was discontinued frequent episodes of desaturation occurred, which responded to manual positive pressure. CPAP was restarted using a high flow air–oxygen mix via a Bennett humidifier on the inspiratory limb and a CPAP valve on the expiratory limb until desaturation ceased. It was decided to provide long term PEEP after withdrawal on a number of occasions led to recurrent episodes of desaturation.

SYSTEM EFFICACY

After the patient was put onto our system and transferred to a general ward, he remained well. His arterial oxygen tension was maintained at between 9 and 11 kPa and his arterial carbon dioxide tension ($Paco_2$) remained in the range of 5·5 to 6·5 kPa. There was no rise in the $Paco_2$ after introduction of the system nor was there any increase in the respiratory rate.

Discussion

There are several of conditions which affect the skeleton and result in abnormal growth of the thorax. The majority of these conditions are rare and experience of management in individual centres is small.

We have been unable to attach an acceptable diagnostic label to this child's collection of dysmorphic features, and any assessment of his future respiratory function can only be guided by general principles. It has been suggested that the natural history of 'small chests' is for the problems to be most severe in the early months of life with gradual resolution if the child survives.[1] The degree of respiratory compromise varies widely between patients even within the same diagnostic groupings.

The rationale for the use of PEEP was to reduce peripheral alveolar collapse and the subsequent ventilation/perfusion mismatch at the end of expiration. The use of long term positive pressure has been previously reported in thoracic dystrophy.[2] In addition to his small chest wall, our patient also has a kyphoscoliosis. In adult patients with this condition lung compliance increases with positive pressure ventilation.[3]

Because the device we have employed uses low flows of oxygen it allows his parents to take the child out of the hospital environment with only a D size oxygen cylinder.[4] It would also be possible to provide flows of this magnitude by using an oxygen concentrator of the type normally used to deliver domiciliary oxygen,[5] so allowing home management.

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CURRENT TOPIC

HIV infection in children

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The World Health Organisation has estimated that 10 million adults and one million children are infected with HIV worldwide.[1] Most of these infections will have been acquried through heterosexual contact and the increasing prevalence of HIV infection among women has implications for children as vertical transmission from mother to child is the major route by which children acquire infection.

The number of children with HIV and AIDS reported in the UK is shown in table 1.[2] There have been no new reports of HIV seroconversion in children with haemophilia since 1985 when blood donor screening for HIV and heat treatment of freeze dried factor VIII concentrate was introduced. This information comes from a multiple of sources including the British Paediatric Surveillance Unit active surveillance scheme, whereby paediatricians are asked to report on a monthly basis any HIV antibody positive children under their care.[3] Recent data from anonymous unlinked test programmes of antenatal women[4] and newborn infants as an indirect measure of infection in pregnant women,[5 6] suggest that HIV prevalence in Scotland ranged from 2·5 per 1000 in Edinburgh, 1·4 per 1000 in Dundee, to 0·7 per 1000 in Aberdeen.[6] In outer London the mean prevalence was one in 1400, in the south east it was one in 16 000,[4] whereas in inner London the prevalence in pregnant women has increased fourfold in the last two years[5] and is now one in 500. In antenatal clinics in other parts of the country only one test in 16 000 was positive.[4]

Vertical transmission of HIV from mother to child

Vertical transmission can occur before, during, or shortly after birth, and the relative contribution of each of these routes is unknown. The European Collaborative Study recently reported a vertical transmission rate of 13% (95% confidence interval 9 to 16%).[7] However, higher rates of transmission have been reported from some African studies.[8] Evidence of the effect of maternal risk factors is scarce, but it has been suggested that the presence of symptomatic HIV disease in the mother, seroconversion during pregnancy, and an increased reliance on clinical diagnosis of HIV in the children may all contribute to the observed higher transmission rates in Africa.[8] Prospective studies have so far not been able to indentify mode of delivery (vaginal or caesarean section) as a risk factor for transmission).

Table 1 HIV infected children in the UK, end of July 1991

	*Born to HIV positive mother (deaths)**	*Haemophilia (deaths)†*	*Blood transfusion (deaths)*	*Total (deaths)*
AIDS	43 (20)	14 (8)	6 (2)	63·(30)
Infected (not AIDS)	54	73 (1)‡	9	136 (1)‡
Total	97 (20)	87 (9)	15 (2)	199 (31)

*Deaths in brackets are **included** in the figures before them.
†Only children who are **under** 15 years of age as of July 1991 are included.
‡One child died of a non-HIV related cause.

Postnatal transmission of HIV may occur via breast milk.[9] However, the additional risk to the child of a woman who is already infected with HIV throughout pregnancy is unknown, although a recent report from Zaire suggests that it is small.[10] In developing countries, where bottle feeding is associated with significant mortality and morbidity, the risk of transmission of HIV via breast milk is much less than the risk of bottle feeding itself.[11 12] Finally, it has been suggested that breast feeding may delay the onset of symptomatic disease in the child infected with HIV.[10 13]

Diagnosis of infection

Diagnosis of HIV infection in a child can be problematic, both in the infant born to an HIV positive mother and in the older child where HIV infection may be part of a wide variety of differential diagnoses.

Children born to HIV antibody positive mothers have no manifestations of infection at birth but all will have acquired maternal antibodies via the placenta and thus test HIV antibody positive at birth. Maternal HIV antibodies persist for a median of 10 months but may be present for as long as 18 months.[7] As antiretroviral drugs and prophylactic antimicrobials become available for early use, the need to develop reliable methods for early diagnosis of HIV infection is becoming increasingly important.

Virological tests including viral culture, p24 antigen and the polymerase chain reaction, which detects and amplifies viral genetic material, are relatively insensitive in the first three months of life.[14] In addition they are costly, time consuming, and not routinely available.

Immunological abnormalities including hyperimmunoglobulinaemia, abnormal T lymphocyte subsets with low CD4 numbers, and an inverted CD4:CD8 ratio may suggest infection,[7] but the normal range of these parameters is poorly defined in infants, and such tests lack specificity. In the European Collaborative Study clinical manifestations that discriminated infected from uninfected children born to HIV positive mothers included oral candidiasis, persistent parotitis, and Gram negative septicaemia or pneumonia.[7] Non-cryptosporidial diarrhoea, lymphadenopathy, fever, and hepatosplenomegaly were relatively non-specific.

In summary, although to date there is no single test that can definitively diagnose infection in the early months of life, by using a combination of virological and immunological tests with clinical examination at regular intervals in the first months of life, it is usually possible to obtain an indication as to whether or not a child is infected.

In the older child, the diagnosis of HIV may be suggested by a wide spectrum of symptoms and signs, many of which are non-specific (table 2). If the paediatrician decides that a child should be tested for HIV infection, informed consent should be obtained from the parents. The issue of pretest counselling is one which many paediatricians find inhibiting because of the distress it causes parents. However, by testing the child, the mother is also being tested, and it is important to discuss the implications of a positive test with the parents before embarking on testing. It is rare that a parent refuses to have a child tested if the child is symptomatic.

Natural history and characteristic manifestations of HIV

The natural history of children infected by transfusion or coagulation factors may differ from that of vertically infected children in both the duration of the incubation period and clinical pattern of disease. In the former group, the time from infection to the onset of AIDS is shortest in infants and older adults and longer in children, adolescents, and young adults.[15] In addition, lymphocytic interstitial pneumonitis (LIP), which effects 30–50% of vertically infected children, appears to be less common in children with haemophilia.[16 17] Thus in both these respects, the disease in children with haemophilia appears more closely to resemble that of adults.

Table 2 Manifestations of HIV disease

AIDS indicator diseases
Opportunistic infections
LIP
HIV encephalopathy
Severe recurrent bacterial infections
Severe failure to thrive
Malignancy
Other manifestations of HIV infection
Persistent/recurrent oral candidiasis
Persistent parotitis
Persistent diarrhoea
Persistent hepatomegaly/splenomegaly
Persistent generalised lymphadenopathy
Thrombocytopenia
Severe/recurrent varicella infection
Nephropathy
Cardiomyopathy

Approximately one third of children with vertically acquired HIV infection develop severe disease in the first year of life. The remainder have a more slowly progressive course, although nearly all show some manifestations of infection (clinical or immunological) by 12 months of age.[7] In retrospective cohorts of children presenting to hospital with HIV disease, determinants of prognosis included both age at diagnosis and presenting symptoms.[18 19] Thus children presenting under 1 year of age with opportunistic infections (mainly *Pneumocystis carinii* pneumonia) or HIV encephalopathy had a poorer survival than those presenting at an older age with bacterial infections or LIP. The highest incidence of *P carinii* pneumonia is in the first few months of life and this may be the first indication that a child is infected; it is associated with a high mortality rate.[20]

Neurological disease due to HIV presents with regression of developmental milestones and/or progressive motor signs, often commencing with a spastic diplegia. The reported prevalence of neurological abnormalities in HIV infected children is higher in USA (50–90%)[21 22] than in Europe (20–30%).[7 19] This may be due in part to methodological differences in patient recruitment, but also to cocaine use in mothers of infected children in USA. The European studies reported abnormalities only after the development of immunosuppression and other severe manifestations of HIV or AIDS.

Recurrent bacterial infections, especially with polysaccharide encapsulated bacteria, have been reported to occur more frequently in children with HIV infection,[23] but there is no evidence that viral respiratory infections occur more commonly.

LIP is a slowly progressive chronic lung disease, characterised by reticulonodular infiltrates on the chest radiograph. The aetiology is unclear, but could involve Epstein-Barr virus[24] or HIV itself; further study is required. Despite abnormalities on the chest radiograph, the child may be asymptomatic initially with no abnormal findings on auscultation. Later shortness of breath, hypoxia, and digital clubbing may develop, although children rarely die of LIP alone. A definitive diagnosis is based on a lung biopsy specimen, but a presumptive diagnosis can be made from the characteristic chest radiograph appearances after other causes of interstitial pneumonitis have been excluded. However, differentiating LIP from other lung disease such as tuberculosis, bacterial infection, and *P carinii* pneumonia is not easy and it is prudent to perform a baseline chest radiograph in any HIV infected child to avoid later diagnostic difficulties.

Surrogate markers for disease progression

In children, markers of progression of disease have been less extensively studied than in adults. CD4 (T helper) lymphocyte counts are age dependent, being higher in infancy, and values have not yet been clearly defined in normal children. Although p24 antigenaemia was not shown to predict progression to AIDS in the first 12 months in the European Collaborative Study,[7] other studies have suggested otherwise.[14] Further research in this area is required as such surrogate markers would be valuable as endpoints in clinical trials, particularly for treatments used in early HIV infection or asymptomatic children.

Management

FOLLOW UP OF THE CHILD BORN TO AN HIV POSITIVE MOTHER

Where a child is born to an HIV positive mother, the paediatrician should ideally have met the mother before the child is born to discuss issues such as breast feeding and difficulties with early diagnosis. The baby should be examined in the neonatal period and virological and immunological investigations performed. In addition, a urine and serum sample should be tested for cytomegalovirus to exclude congenital infection, and where maternal hepatitis B carrier status is unknown, hepatitis B status should be determined. At this time discussion about informing the general practitioner and health visitor if they do not already know should take place. Most mothers recognise the value of this, but are afraid that the information will be further disseminated to others. Good liaison between community and hospital personnel with discussion about confidentiality issues is important. In some circumstances the possibility of shared care with a specialist centre may be considered. Finally, as HIV may affect a number of family members, family centred care where all members of the family can receive medical and social care and follow up needs consideration. The role of 'family clinics' is likely to increase in the future.

Infants should be followed up at regular intervals of three months to identify any early manifestations of disease or immunosuppression and to determine the child's infection status. The mother, general practitioner, and health visitor should be aware that every referral is important if the baby becomes unwell, especially with respiratory symptoms suggestive of *P carinii* pneumonia.

MANAGEMENT OF THE CHILD WITH HIV INFECTION

The mainstay of management is close follow up in a multidisciplinary setting with prevention of infections by prophylaxis and vaccination, prompt treatment of bacterial and opportunistic infections, and if necessary, early nutritional support to prevent failure to thrive.

Table 3 Guidelines for prophylaxis against P carinii pneumonia in paediatric HIV infection[27]

Age	*CD4 count ($10^9/l$)*	
1–11 Months	<1·50	
12–23 Months	<0·75	
2–6 Years	<0·50	
>6 Years	<0·20	
Drugs		
Co-trimoxazole	Trimethoprim 150 mg/m^2 Sulphamethoxazole 750 mg/m^2	Daily or three times weekly
Pentamidine	300 mg via Respigard II nebuliser	Monthly
Dapsone	1 mg/kg	Daily

VACCINATIONS

The baby should receive all routine vaccinations including measles vaccination, at the normal time, and hepatitis B vaccine when indicated. It is preferable to give killed rather than live polio vaccine, because of the theoretical risk of transmitting live polio virus to other immunocompromised family members. No adverse effects have been observed from either measles or live polio vaccines in HIV infected children. If the baby proves to be infected, vaccination against haemophilus and meningococcus is advisable. It has been demonstrated that asymptomatic children with HIV infection produce satisfactory antibody responses to measles vaccination but these may decrease with declining immune function,[25] so that immunoglobulin prophylaxis may be required after contact with measles or chickenpox. BCG should not be given to HIV symptomatic children, but there have been no adverse effects reported from giving it in the neonatal period to children subsquently found to be HIV infected.[26]

Prophylaxis

P CARINII PNEUMONIA

Prophylactic treatment for *P carinii* pneumonia has not been evaluated in children with HIV infection. Extrapolating from adult data and from studies of *P carinii* pneumonia prophylaxis in children with leukaemia, co-trimoxazole (Septrin, Wellcome) given three times weekly is the drug of choice. However, in vertically infected children the incidence of *P carini* pneumonia is high early in life, often before a definitive diagnosis of infection can be made. For example, six of the eight children reported with *P carinii* pneumonia in the UK developed the disease in the first six months of life, and six have died (C Davison, personal communication). Furthermore, whereas in adults *P carini* pneumonia is rare if the CD4 count is above $0{\cdot}2\times10^9/l$, it can occur in children with CD4 lymphocytes over $1{\cdot}0\times10^9/l$. Guidelines for *P carinii* pneumonia prophylaxis in children, based on CD4 counts, have been recently issued (table 3).[27] Where such tests are not available, prophylaxis should be considered in any infected infant. For older children, phase studies of pentamidine administration, using a modified Respigard II nebuliser, are commencing in the USA.

BACTERIAL INFECTIONS

Theoretically, immunoglobulin treatmen provides passive antibody to protect against a wide range of infections. A recent US multicentre, placebo controlled trial of monthly immunoglobulin reported a decreased incidence of bacterial infections, particularly invasive pneumococcal disease and clinically diagnosed acute pneumonia, but no reduction in mortality.[23] The authors commented that these results should not be interpreted as indicating that all children with HIV infection should receive immunoglobulin. Further evaluation is required to identify those children most likely to benefit. In the mean time, the risk o bacterial infection in an individual child must be weighed against the disadvantages of frequent hospital attendance and regular insertion of cannulae. It is possible that daily co-trimoxazole prophylaxis, in addition to preventing *P carinii* pneumonia, may be a useful prophylaxis against bacterial infections.

Antiretroviral therapy

The only antiretroviral drug currently available for treatment of children with HIV infection is 3′-azido-3′-deoxythymidine (AZT), although dideoxyinosine (DDI) and dideoxycytosine (DDC) are being evaluated in phase I studies in USA. AZT inhibits viral reverse transcriptase activity and has been shown to prolong life in symptomatic adults. It has also been shown to slow disease progression in asymptomatic adults with CD4 lymphocytes below $0{\cdot}5 \times 10^9$/l.[28] There have been no studies of its efficacy in children but phase I and II studies in symptomatic children have suggested an increase in weight and well being and an improvement in HIV encephalopathy.[29] The criteria for commencement of treatment with AZT and at what dose remain unclear and practices vary widely. For this reason, a multicentre trial to answer these questions about AZT is to commence in Europe in the near future. This would be rapidly followed by other studies comparing monotherapy with combinations of antiretroviral drugs as well as trials of prophylactic drugs.

Conclusion

The prevalence of HIV infection in women and children is increasing and paediatricians need to become familiar with the disease. Although in the UK the size of the problem is still limited, the number of infected children is increasing. Now is the time to consider the organisation of services to provide regular, coordinated follow up of children born to HIV positive mothers as well as other family members. The issue of early diagnosis needs to be addressed, and collaboration with other European centres is needed to set up clinical trials for evaluation of antiretroviral and antimicrobial prophylactic treatments. Although some HIV infected children develop severe disease early in life, in many disease progression is slow. There is no evidence of casual transmission of HIV occurring in the school or playgroup setting[30] and children with HIV can attend as normal children do. Paediatricians need to be involved in dispelling the stigma and fear which surrounds this disease and enable children and their families with HIV to live as full lives as possible.

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REGULAR REVIEW

Medium chain acyl-CoA dehydrogenase deficiency

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Abstract

From 65 reported cases of medium chain acyl-CoA dehydrogenase deficiency, we found an average presenting age of 13·5 months and a mean age at death of 18·5 months. One quarter of patients died of a Reye-like syndrome and/or sudden infant death. In half the cases there had been at least one sibling death. Asymptomatic cases were not uncommon (12% of cases). The crises were generally induced by a prolonged fast and after a viral prodromal phase in three quarters of cases. The crises consisted of somnolence progressing to lethargy which could lead to coma. Vomiting was frequent (60% of cases). Seizures, which were found in 29% of cases, represented a bad prognosis. The physical examinations revealed frequently a variable and regressive anicteric hepatomegaly.

Blood and urine analysis revealed in most instances hypoglycaemia (96% of cases) with hypoketonuria and sometimes metabolic acidosis. Hepatic and muscular cytolytic enzymes were frequently raised, as were plasma ammonia, urea, and uric acid. Plasma total or free carnitine concentrations, especially non-fasting, were diminished in most cases. Plasma saturated medium chain fatty acids and particularly unsaturated *cis*-4-decenoate were on the other hand raised during the crises or during fasting. Urinary organic acid analysis revealed a characteristic profile of medium chain aciduria: C_6–C_{10} dicarboxylic acids, hydroxy acids, glycine conjugates, and carnitine conjugates. Oral loading tests with carnitine or phenylpropionate allow a precise diagnosis. The diagnosis is confirmed by specific assays in various tissues. Avoidance of prolonged fasting seems to be the mainstay of treatment.

Fatty acid oxidation plays an important part in maintaining energy homoeostasis during fasting. Deficiency of medium chain acyl-CoA dehydrogenase (M-CAD)[1] was recently recognised as the most common hereditary disease of hepatic fatty acid oxidation and one of the commonest inborn errors of metabolism.[2] The incidence is estimated at 1/20 000 newborn infants and more than 85 patients have now been reported, in 65 of whom the diagnosis has been confirmed enzymatically.[3] This enzymatic defect was first suspected in 1976[4] and was initially reported as 'hypoketotic hypoglycaemia with C_6–C_{10} dicarboxylic aciduria' related to fasting.[5–8] M-CAD deficiency has been reported in Reye-like syndromes.[9 10] It is also recognised in familial and recurrent Reye's syndrome,[11 12] particularly in the first two years of life. M-CAD deficiency has been demonstrated in some cases of sudden infant death syndrome (SIDS).[13–17] Disease entities previously reported as systemic carnitine deficiency[18 19] have been recently demonstrated to be cases of M-CAD deficiency.[20–22]

The specific diagnosis of M-CAD deficiency was initially made in patients with an acute onset of the disease[23]; although more difficult, the diagnosis is now made in asymptomatic children.[16] The diagnosis has been mainly based on plasma and urinary organic acid analysis by means of gas chromatography and mass spectrometry (GC-MS).[24] The outcome may be fatal in the absence of appropriate therapeutic management.

In this general survey of the published patients with M-CAD deficiency, we discuss the principal features of this recently recognised enzymatic defect.

Results and discussion

CLINICAL FEATURES (table 1)

The average age for the first presenting episode in M-CAD deficiency was 13·5 months and varied between 2 months and 4 years. There was an equal distribution between the sexes (27 males and 26 females). The mortality rate was one quarter of the studied cases. Roe *et al* find the mortality rate as high as 60% for a first episode between the ages of 15 and 26 months.[3] The mean age at death was 18·5 months. The Reye-like syndrome and/or SIDS were the causes of death. In half the families studied, one or more previous sibling deaths had occurred.

*Table 1 Clinical information in 65 M-CAD deficient patients**

		%	*Range (months)*
Patient's history			
Sex distribution (M/F)	27/26		
Mean age of first episode (months)	13·5		2–48
Mortality rate	14/53	26	
Reye-like syndrome	12		
and/or SIDS	11		
Mean age at death (months)	18·5		7–30
Previous sibling death	16/33	48	
Presenting symptoms and signs			
Somnolence, lethargy, or coma	57/57	100	
Viral prodrome	34/46	74	
Vomiting	28/47	60	
Seizures	14/48	29	
Hepatomegaly			
Frank	12/32	38	
Total	19/32	59	
Asymptomatic	8/65	12	

*Only information recorded for each patient is indicated. Four neonatal cases were not included.

The main presenting symptom of M-CAD deficiency was somnolence in 100% of symptomatic cases, progressing to lethargy which could lead to coma. This symptom was induced by fasting for longer than 12 hours. A viral prodromal episode, comprising mainly digestive and respiratory symptoms, was found in three quarters of the cases studied. Vomiting was frequent (60%). Seizures, which were less frequent (30%), indicated a poorer prognosis: six deaths and two cases of epilepsy were noted among the 14 patients with seizures. Frank hepatomegaly was noted in 38% of cases. Asymptomatic cases were not uncommon (12%).

It is important to note the absence of any delay in psychomotor development and growth, and the absence of clinical myopathic manifestations in the heart and skeletal muscles, such as frequently encountered in long chain acyl-CoA dehydrogenase deficiency.[25] Previous acute crises and recurrences are frequent in M-CAD deficiency.[20 21]

Table 2 Plasma values at presentation in M-CAD deficient patients

Investigation	*No (%) with abnormal result*	*Range or value*	
		Patients	*Controls*
Glucose (mmol/l)	45/47 (96)	0·10–0·25	3·3–5·5
β-hydroxybutyrate ×glucose (mmol²/l)	5/5 (100)	0·17–3·70	9–14[15]
Free fatty acid: β-hydroxybutyrate (fasting)	10/10 (100)	1·4–56	<1[27]
Carbon dioxide (mmol/l)			
Moderate acidosis	7/23 (30)	11–15	21–28
Mild acidosis	9/23 (39)	16–19	
SGOT (U/l)*	17/19 (90)	43–924	<40
SGPT (U/l)*		48–696	<40
Ammonia (µmol/l)			
Moderate hyperammonaemia	9/18 (50)	>100	<60
Mild hyperammonaemia	5/18 (28)	>60	
Uric acid (µmol/l)	7/7 (100)	565–1428	<450
Urea (mmol/l)	8/9 (89)	7–28	<6·5
Lactate dehydrogenase (U/l)	3/3 (100)	503–1260	<250

*SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; SGOT and/or SGPT were measured.

Table 3 Concentrations of plasma carnitine and medium chain fatty acids in M-CAD deficiency

	No (%) with abnormal result	*Range or value*	
		Patients	*Controls**
Remission, fed state			
Carnitine (µmol/l)†	21/22 (96)		
Total		7–36	40–60
Free		3–24	42±8
Acute, fasting state‡			
Carnitine (µmol/l)	10/13 (77)		
Acylcarnitine:free carnitine ratio	7/8 (88)	⩾0·5	<0·5
Octanoate (C_8, µmol/l)	18/18 (100)	8–394	ND
Decanoate (C_{10}, (µmol/l)	14/16 (80)	7–96	ND
Cis-4-decenoate (µmol/l)	15/15 (100)	3–168	ND

*Reference values.[1 23]
†Other references indicate: total carnitine 5–23 µmol/l in nine patients,[21] free carnitine 1–24 µmol/l in 15 patients.[26]
‡Including fasting tests.
ND, not detected.

Table 4 Main urinary metabolites in M-CAD deficiency

	No (%) with abnormal results	*Range (µmol/mmol creatinine)*	*Controls**	
			Fasting	*Ketosis*
Ketones (ketosticks)	18/21 (85)	Negative to +	⩾++	
↑ Dicarboxylic acids (in acute state)				
Adipate C_6	41/43 (95)	+ to ⩾50	<15	<300
Suberate C_8	41/42 (98)	+ to ⩾40	<13	<50
Sebacate C_{10}	37/39 (95)	+ to ⩾30	<11	<18
↑ Hydroxy acids				
5-Hydroxyhexanoate C_6	20/21 (95)	+ to ⩾50	<10	
↑ Glycine conjugates (in acute state or remission)				
Hexanoylglycine	25/28 (90)	+ to ⩾10	<1	<1
Suberylglycine	27/27 (100)	+ to ⩾9	<2	<2
Phenylpropionylglycine†	24/25 (96)	0·6–98	<0·6	
↑ Carnitine conjugates				
Octanoylcarnitine‡	26/26 (100)	+ to ⩾4	<1	

*Age: 1 day–15 years (n=70) receiving regular diet with no supplementary medium chain triglycerides.[24]
†21 Patients accurately identified with stable-isotope dilution assay.[28]
‡12 Patients exclusively identified by FAB-MS.[30]

PLASMA FEATURES (table 2)

During the crises, hypoglycaemia was constantly present (96%). Plasma β-hydroxybutyrate was disproportionately low given the hypoglycaemia, thus defining a hypoketotic hypoglycaemic state. M-CAD deficiency was characterised by a deficient ketogenesis, demonstrated by an abnormal (high) free fatty acids:ketone bodies ratio during fasting in all analysed cases. Moderate metabolic acidosis was found in 30% of the studied cases. Plasma transaminases concentrations were almost always raised. This increase has sometimes been progressive with the appearance of a secondary hepatomegaly.[11] There was moderate hyperammonaemia in half the cases. Plasma uric acid, urea, lactate dehydrogenase, and creatine kinase were also frequently at high concentrations during the crises. The prothrombin time was sometimes diminished (3/7) and plasma bilirubin was normal.

M-CAD deficiency is generally characterised by secondary carnitine deficiency and abnormal high acylcarnitine:free carnitine ratios (table 3).[26] In the fed state, free or total carnitine were almost always at low concentrations in the plasma, thus defining a permanent hypocarnitinaemic state. In acute crises, or in fasting tests, hypocarnitinaemia was found in 77% of cases, less frequently than in the fed remission state. In six untreated M-CAD deficient patients[3] tissue carnitine concentrations in muscle and liver are about 25% of normal. The acylcarnitine:free carnitine ratio was abnormal in seven out of eight cases during the crises or fasting tests. This parameter seems to be the best indicator of symptomatic M-CAD deficiency. There was a constant high concentration of saturated octanoate and especially unsaturated *cis*-4-decenoate in plasma during crises or fasting tests. *Cis*-4-decenoate detection is considered to be pathognomonic of M-CAD deficiency and is not influenced by dietary supplementation with medium chain triglycerides.[27]

URINARY FEATURES (table 4)

Hypoketonuria was found in 85% of cases. The analysis of urinary organic acids by GC-MS during the acute episodes revealed a C_6–C_{10} dicarboxylic aciduria (C_6 adipate, C_8 suberate, C_{10} sebacate) and a monocarboxylic (omega-1) hydroxylated aciduria (5-hydroxyhexanoate). These metabolites are produced by the deviation of fatty acid oxidative metabolism towards alternative microsomal pathways. This urinary profile is characteristic of M-CAD deficiency.[24]

Specific metabolites of M-CAD deficiency (especially hexanoylglycine, suberylglycine, and phenylpropionylglycine) are found and quantified during the crises and remissions using recent sensitive assays, especially the stable isotope dilution measurement.[28] This assay allows the differential diagnosis between M-CAD deficient infants and normal infants receiving formulas supplemented with medium chain triglycerides.[29] Urinary medium chain acylcarnitines, especially octanoylcarnitine, are also found in the analysed cases, mainly using fast atom bombardment mass spectrometry (FAB-MS).[30]

PATHOLOGICAL FEATURES

Panlobular microvesicular macrovesicular hepatic steatosis was generally present in M-CAD deficient patients during the acute crises. Ultrastructural analysis of hepatic mitochondria may differentiate M-CAD deficiency from idiopathic Reye's syndrome, mainly by a condensed matrix appearance with widening of the intracristal spaces.[21]

IN VIVO DYNAMIC TESTS

Fasting tests revealed M-CAD deficiency by the detection of specific plasma and urinary metabolites. These tests are potentially dangerous, as shown by eight out of 16 cases where serious clinical manifestations were provoked, including lethargy, one case of coma after only 12 hours of fasting[31] and one case of death.[4] These clinical manifestations are not necessarily correlated with hypoglycaemia.[20 32]

Oral loading tests with lipid and medium chain triglycerides were also potentially dangerous, inducing neurological deterioration in two cases,[8 11] and an aggravation of hepatomegaly in one case.[10] Oral loading with carnitine (100 mg/kg) helped in establishing the diagnosis of M-CAD deficiency, with no risk to the patients, by the detection of urinary octanoylcarnitine.[16 30]

The phenylpropionic acid oral loading test is based on the fact that phenylpropionate is oxidised by the M-CAD enzyme to benzoic acid, which is then excreted in the urine as hippuric acid.[33] After oral loading with phenylpropionate (25 mg/kg), control subjects and parents excreted only hippurate, whereas the urinary metabolites of M-CAD deficient patients consisted of approximately one third phenylpropionylglycine and two thirds hippurate.[34 35]

IN VITRO TESTS

Enzymatic diagnoses were first performed by a global assay of fatty acid oxidation in intact cultured fibroblasts.[36 37] This procedure consists of measuring liberated carbon dioxide from 1-^{14}C fatty acid substrates of varying chain length (C_{16} palmitate, C_8 octanoate, C_4 butyrate) in order to determine the specific enzymatic activity for the three acyl-CoA dehydrogenases (long, medium, and short chain ACD) involved in mitochondrial β-oxidation. In M-CAD deficiency, the mean enzymatic activity with 1-^{14}C octanoate as substrate varies between 10% and 29% of normal (n=21).[38]

The specific enzymatic dosages[3] have been obtained in hepatocytes, fibroblasts, peripheral mononuclear leucocytes, cardiac myocytes, skeletal myocytes, and amniocytes. In M-CAD deficiency, the specific enzyme activity measured with octanoyl-CoA as substrate is between 3% and 10% (n=40) with a mean of 6%.[3]

The molecular studies confirmed a single prevalent point mutation consisting of lysine to glutamate substitution on chromosome 1.[39] This point mutation is present in more than 90% of the alleles[40] and could represent a highly distinctive feature of M-CAD deficiency.

POSTMORTEM RECOGNITION

M-CAD deficiency should be suspected after unexpected death in infancy and death from Reye's syndrome. Specific postmortem diagnosis may be made by the finding of raised concentrations of plasma *cis*-4-decenoate[27] and the detection of urinary or hepatic octanoylcarnitine by FAB-MS.[41] Specific enzymatic assays in various frozen tissues led to the diagnosis of M-CAD deficiency in SIDS.[42]

Retrospective studies estimate the frequency of M-CAD deficiency in the SIDS population at about 1–2% in England[14 17] and possibly also in France (1/110) (P Divry, personal communication).

PRENATAL DIAGNOSIS

Prenatal diagnosis has already been achieved in a sibling of a SIDS case with M-CAD deficiency, and later confirmed in the neonatal period.[43]

TREATMENT

During the crises, symptomatic treatment is necessary to overcome the hypoglycaemia, cerebral oedema, seizures, or metabolic acidosis. The mainstay of treatment of M-CAD deficiency is the prevention of an acute episode by avoiding prolonged fasting periods and by providing glucose supplementation.[2 32] A low fat diet is not necessarily recommended.[12] L-Carnitine administration (100 mg/kg/day) is considered to be beneficial,[30 31] but this is contested by some authors who did not find an improvement in fasting—induced ketogenesis after L-carnitine supplementation.[32 44] Carnitine seems to be important in the elimination of potentially toxic metabolites accumulating after enzymatic block. This is recently confirmed by the finding of a greater excretion of medium chain acylcarnitines after L-carnitine administration.[45]

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PERSONAL PRACTICE

Lower oesophageal pH monitoring—a useful clinical tool

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Early diagnosis and prompt treatment of gastro-oesophageal reflux (GOR) can halt unnecessary investigations and prevent medical complications, such as failure to thrive,[1] severe oesophagitis,[2] and aspiration syndromes.[3] The standard investigation for GOR is the upper gastrointestinal barium contrast series. However, because of poor sensitivity and specificity the role of this test in clinical practice has been questioned.[4] Several other methods of investigation are available and to some extent the choice of investigation depends on the clinical problem.[5] Over the last 10 years, 24 hour lower oesophageal pH monitoring has increasingly become established as the 'gold standard' for documenting 'acid' GOR.[3 5] The ability to monitor over prolonged time intervals and the avoidance of any radiation are particularly attractive features of this test. However, until recently, the use of the technique has largely been confined to clinical research studies. At the Royal Hospital for Sick Children (RHSC), Glasgow, over the last four years an open clinical pH monitoring service has been available and has proved valuable in diagnosing and managing GOR. We describe here the development of this service, our experience with the technique, and our current practice.

Setting up the service

We first used pH monitoring as a research tool between 1984 and 1986 at the RHSC. The test was increasingly used for diagnostic purposes and in 1986 we established a clinical service. This service was routinely available to all consultants in the hospital and any paediatricians referring children from district paediatric facilities in the west of Scotland. Initially, the clinical studies were performed by medical staff (JYP) but by 1988 the senior NHS technician (CK) in the respiratory laboratory had been trained in the technique. Since then she has been responsible for all technical aspects of the monitoring.

Equipment

All pH studies are performed using a Synectics Digitrapper System for ambulatory pH recording (Synectics Medical Ltd). pH measurements from a 3 mm antimony probe sited in the lower oesophagus are measured every four seconds and stored electronically in the Digitrapper memory. After the completion of a study readings are downloaded from the digitrapper to an IBM AT computer, using dedicated software, for analysis and storage on disc.

Lower oesophageal pH measurement

Each study is performed in hospital by one experienced technician (CK). Initially, the pH probes were passed by ward nurses but latterly, this too has been performed by the technician. Currently, in a large paediatric teaching hospital we perform between three and six studies per week. Each study takes approximately 30 minutes to set up and 15 minutes at the end to analyse. Reporting is performed by one paediatrician (JYP).

Performing the study

No premedication is used so that the 24 hour recording can include as much normal activity as possible. If children are admitted specifically for the investigation it is commenced in the afternoon and they are discharged the next evening. During the 24 hours of the study the children are allowed normal diet and unrestricted activity. The child's carer is asked to note the time of events such as the beginning and end of feeds on a chart and to activate an electronic marker by pressing a button on the recorder. In a busy ward setting it has not proved practical to note accurately either the child's position or state of arousal from minute to minute.

Before use and between studies, the probes are sterilised by immersion in 70% methylated spirit for four hours. Then the probe is calibrated in vitro using standard buffer solutions (pH 7·0 and 1·01, Synectics Medical) at 23°C.

At the start the procedure is explained to parents and child. Each child's height is measured and the distance from the tip of the nose to the lower oesophageal sphincter calculated using the nomogram of Strobel *et al*,[6] which relates oesophageal length to height. A distance, equal to 87% of the total, is calculated and marked on the pH probe which is then passed to this mark. This places the probe above the lower oesophageal sphincter. As there is no fixed radiographic landmark for the lower oesophageal sphincter we have not routinely confirmed the position of the probe by radiography. However, a number of children have had chest radiographs while the probe was in place and in each case the probe has been situated in the lower oesophagus above the diaphragm as expected.

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Once fixed in position the probe is then connected to the recorder (Digitrapper). This is small, battery operated, and portable allowing unrestricted activity. When the study is completed the data in the electronic recorder is transferred to a computer and the recording reviewed; if technically satisfactory, the child is discharged home.

Analysis of pH studies

The study is initially reviewed on computer screen by the technician. The timing of any periods of artefact during the study are noted and can then be disregarded in the subsequent analysis. The duration of the study and the following indices of GOR are then calculated automatically by the computer software and are used to describe the study: (i) the number of episodes of reflux, (ii) the number of episodes of reflux lasting greater than five minutes; (iii) duration of the longest episode, and (iv) percentage of the total time where the pH was less than 4 (reflux index). All indices are normalised to a 24 hour baseline to compensate for differences in study lengths between subjects. A printout of each study with the results and a 24 hour graph is produced for the child's notes.

Costs

One pH probe costs £35 and can be reused on a limited basis. On average we have been able to perform seven studies with each probe. When a probe fails to calibrate at the beginning of a study it is replaced.

The current capital cost of a system including the Digitrapper, accessories to perform 30 studies, and computer software (running on an IBM compatible computer) is £4500. The digitrapper recorders very occasionally need repair reflecting the heavy use they receive.

Clinical experience with pH monitoring

To audit the service we performed a retrospective analysis of consecutive studies performed between April 1985 and March 1989. The children studied could be divided into two broad categories reflecting the medical and surgical situations where GOR is commonly suspected: normal infants with vomiting and children with underlying neurological problems where GOR is common but the diagnosis often difficult (table).

In the four year period 229 studies were performed on 152 children referred by physicians and surgeons in RHSC. Fifty one children had underlying neurological disease while 101 were neurologically normal. Twice as many boys as girls were studied in all groups. Children with underlying neurological disorders were generally older than the other normal children.

Indications for pH monitoring

The clinical problems prompting a request for a pH study are listed in the table. Gastrointestinal symptoms, particularly vomiting, dominated. Within the group of normal children the second main reason for requesting a study was failure to thrive. In contrast, among children with neurological problems the second commonest indication was unusual neurological presentations, such as seizure-like episodes which have been reported to be related to GOR.[7] Respiratory problems possibly related to recurrent pulmonary aspiration, secondary to GOR, were another common indication in both groups.

Symptoms in children suspected of GOR referred for pH study

	Neurological (n=51)	*Non-neurological (n=101)*
Gastro-intestinal:		
Vomiting	21	60
Haematemesis	7	10
Abdominal/chest pain	3	5
Anaemia	1	2
Dysphagia	0	2
Failure to thrive	1	21
Respiratory:		
Lower respiratory tract	6	8
Wheeze	5	8
Apnoea	2	6
Choking	2	11
Neurological:		
Irritability	4	1
Seizures	13	0
Others	3	3

Acid reflux

In the studies we defined an episode of reflux as occurring when the oesophageal pH fell below pH 4. This is the level most commonly used to define 'acid' GOR since Tuttle and Ruffin showed that adult volunteers experienced epigastric pain from infused acid solutions below pH 4.[8] Also in vitro work shows pepsin to be inactive in solution above pH 4. However, there is no directly similar data available for children. pH 4 may not always be the most appropriate level to use particularly in young children. For example, Mason showed that the pH of gastric contents took some time to fall below pH 4 in breast fed neonates.[9] When using pH 4, therefore, to indicate reflux it is important to remember that non-acid reflux may occur and will not be detected. It is, therefore, useful to look for short episodes of brief physiological reflux at some point during a study as confirmation that sufficient acid is being produced.

Reporting

In reporting we used the normal values of Vandenplas and Sacre-Smits[10] and Biox-Ochoa *et al.*[11] The series of Vandenplas and Sacre-Smits of lower oesophageal pH studies in 285 asymptomatic siblings of children dying of sudden infant death syndrome represents the largest series of 'normal' data available for children. Clearly some caution must be exercised in viewing such a group as 'normal'.

Vandeplas and Sacre-Smits found between 0 and 15 months of age normal values for reflux index of up to 11·5% and up to eight episodes of reflux lasting more than five minutes during a 24 hour study (mean+2SD). For older children normal values were: a reflux index up to 6% and up to six episodes of reflux lasting more than five minutes (mean+2SD).

In reporting the studies, we initially focused on the reflux index and the number of pH drops longer than five minutes over a 24 hour period. These are the two indices identified by Euler and Byrne as providing the best discrimination between normal and abnormal 24 hour pH studies.[12] In practice, however, we have found little gain in using the combination of parameters. The percentage time pH is less than 4 in the lower oesophagus (reflux index) has provided a convenient single summary of the study for clinical purposes. Hampton *et al* have also recently reported no apparent advantage in using variables other than the reflux index.[13]

Results

Using the data from Vandeplas and Sacre-Smits for classifying the studies, 82 children (56%) were judged to have 'significant' GOR.[10]

Oesophageal pH monitoring proved particularly useful in children with underlying neurological problems where more than half the children studied had pathological GOR. In these children the presence of GOR is often difficult to establish by barium studies; some may not even be able to swallow reliably for the study to be performed. In contrast, many are used to having nasogastric tubes in place and the presence of a pH probe causes little additional distress. Without pH monitoring, confirming the diagnosis of GOR in these children would often have been difficult.

Repeat studies

One advantage of pH monitoring is the opportunity to repeat studies on a number of occasions. In the period reviewed we repeated studies for four main reasons: to confirm an unexpected or important result, to evaluate the response to treatment, to assess if natural resolution of GOR had occurred with time, or because of technical failure on the initial study (usually disconnection of the probe from the recorder). We did not attempt to investigate systematically the question of reproducibility of pH monitoring, an area recently addressed by Hampton *et al.*[13] In our clinical experience the investigation has been reproducible and changes in pH mirror changes in symptomatology. For example, in 14 children where GOR was diagnosed, a second study was performed after medical or surgical treatment. In seven a clinical improvement was noted and in six of these there was improvement of greater than 6% in the reflux index. In the other seven there was no improvement in either the clinical symptoms or the pH indices of GOR.

We have found lower oesophageal pH monitoring particularly useful in demonstrating the effectiveness of treatment in children with neurological problems where changes in symptoms may not be immediately obvious.

Problems

(A) FAILURES

In 31 studies the procedure failed (14%). In 16 this was due to accidental disconnection of the probes from the recorder, in five to a broken probe, and in four to malposition of the probe. In the remaining six the reasons for the failure were not recorded. Technical failures were readily identifiable allowing the study to be immediately repeated. Hence, despite the fact that the studies are being performed on active and unrestrained children we have found the equipment and technique remarkably robust in routine use.

(B) COMPLICATIONS

No serious complications occurred. In one subject persistent coughing developed at the start of the study. A chest radiograph showed the probe lodged in the right main bronchus. The probe was removed with resolution of the symptom and the study repeated successfully without further morbidity. Other groups have described complications including aspiration of stomach contents and perforation if a stricture is present in the oesophagus. We have not had problems with aspiration and feel perforation is very unlikely when an experienced technician performs the procedure.

Conclusion

We have found lower oesophageal pH monitoring to be a simple and useful tool in the clinical investigation and management of children with suspected GOR. In general, we have found the equipment and technique for pH monitoring surprisingly robust even when used in active or handicapped children.

In this hospital, ambulatory lower oesophageal pH monitoring is increasingly becoming the technique of choice for the initial investigation of suspected GOR in children, particularly when there are associated neurological problems. We feel it is a technique that should now be more widely available and more readily used in clinical paediatric practice.

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3. Estimation

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If (as I suggested in note 2 of this series) significance testing often fails to get the essential information out of a body of data, what alternative statistical approaches are there which might be more effective? Some possibilities can be derived by considering the types of question that medical research workers are aiming to answer. Often these questions relate to a new treatment, and it might be supposed that the appropriate question would be 'Is the new treatment *effective*?'—is the average effect of the treatment (over and above that of a placebo or a standard treatment) different from zero? In fact, such a question is seldom adequate. Usually the question a clinician wants an answer to is more likely to be 'Is the new treatment *effective enough*?'— is the average effect of the treatment large enough to make it worth adopting, having regard to cost, side effects, etc? The question asks not merely whether the effect is different from zero but rather how large its size is, and the answer will be quantitative rather than 'yes' or 'no' or even 'probably'.

Suppose we are looking at a treatment intended to increase the forced expiratory volume in one minute (FEV_1) in asthmatic patients, and a well conducted trial gives us a sample average effect of +0·521 with a standard error of 0·10. The effect amounts to no less than 5·2 standard errors and is very highly significant by any reckoning; the probability of obtaining such a large result if the true average effect is equal to zero is vanishingly small, and in this sense the treatment is almost certainly having a non-zero average effect on FEV_1. But how large is this average effect? In statistical terms, what can we say about the mean of the population of patients from which our sample has been drawn (and which we reckon will contain the future candidates for the new treatment)? Surely, more than the mere statement that it is different from zero. What we would like is some kind of *estimate* of how large the population mean might be in the light of our data.

If one's arm were twisted hard enough, it would be tempting to say that the population mean was 0·52, equal to that of the sample. In statistical jargon, this single number is a *point estimate* of the quantity we are interested in. In a certain sense it is the best point estimate we can achieve, the one most likely to be close to the truth. But it is clearly far from satisfactory—there is no reason at all to believe that the population mean and the mean of the actual sample should be exactly equal. We ought to take other possibilities into account.

If then we have to consider other numbers as possible point estimates, what numbers might be acceptable? One possibility that can be quite confidently ruled out is zero. We have seen that our sample mean differs very significantly from zero—if the population mean really is equal to zero, a sample mean as large as that which we have actually observed would be extremely improbable. Zero is not an acceptable estimate of the population mean.

So 0·52 is a possible point estimate and zero is not. What about some intermediate values, 0·20 say, or 0·40? Taking the first of these as a null hypothesis, the deviation of the sample mean from the hypothetical value amounts to 0·32 which is 3·2 standard errors, corresponding still to a very small significance probability. This hypothetical value also renders the actual sample mean too improbable for it to be acceptable as a point estimate. But a population mean of 0·40 gives a deviation of 1·2 standard errors and a significance level of around 0·23, not a very small probability—if the population mean is equal to 0·40, a sample mean as large as 0·52 will occur quite frequently.

Thus any assumed value for the poulation mean attaches a significance probability to the observed sample mean. We might say that the sample is 'reasonably consistent' with the assumed value if this significance level is not too small. Let us agree to insist upon a particular significance level, α say, to define 'not reasonably consistent'. We can then calculate a range of values such that the sample mean is 'reasonably consistent' with any population mean within the range, in the sense that any such population mean gives the sample mean a significance level greater than α. This range of values is called a *confidence interval* for the population mean, specifically a $100(1-\alpha)\%$ confidence interval, and its extremities are called *confidence limits.* As a matter of detail, the confidence limits for the mean of a Normal population can easily be calculated as:

$$\text{sample mean} \pm (t \times \text{standard error})$$

where t is the appropriate value of Student's t. The 95% limits correspond to the 0·05 level of significance and the corresponding value of t is close to 2 except in very small samples.

It will be appreciated that the width of the confidence interval depends upon the degree of confidence demanded. If we are content with 90% confidence (a significance level of 0·10), a relatively narrow range of values will result; if we demand 99% confidence, more extreme values of the population mean cannot be ruled out and the interval will be that much wider.

The confidence intervals for Normal means described above are symmetric about their central value. This is not an essential property; indeed, by using one tailed significance tests it is possible to construct one sided confidence intervals which extend to infinity in one direction. These are not often called for, but asymmetric intervals are appropriate when the underlying distribution is itself asymmetric or skew. Such intervals are produced when data are analysed after logarithmic transformation and the results are transformed back to the original scale for presentation purposes—odds ratios from 2×2 tables are often treated in this way. I intend to discuss data transformation later in this series.

It is clear that a confidence interval is vastly more informative than a mere significance test. Still with a standard error of 0·10, suppose that the sample mean effect is 0·22. This is 2·2 standard errors away from zero, giving a significance probability of around 0·03, beyond the conventional 5% level. Yet the 95% confidence interval is from 0·02 to 0·42, and the trial data are 'reasonably consistent' with a population average which is too small to be of any practical interest.

The added information is even more apparent when the sample mean does not attain the conventional significance level at $p=0{\cdot}05$. With a standard error of 0·10, a sample mean of 0·18 gives a 95% confidence interval from −0·02 to +0·38. We cannot at this level of confidence assert an effect which is definitely positive; but we can rule out values of the population mean that are seriously negative and see that the true effect may in fact be quite substantial, ample information to justify further investigation. On the other hand, a very large trial giving a sample mean of +0·03 with a standard error of 0·02 provides a 95% confidence interval from −0·01 to +0·07, showing not only that zero is an acceptable value for the population mean but (much more importantly) that any true effect in either direction is likely to be quite small. We have, with 95% confidence, established the 'quasi-null' hypothesis that the true mean effect is 'nearly' equal to zero.

There is one important defect in the confidence interval approach that has been illustrated in the previous paragraph. It is possible (and very desirable) to play down the malign influence of the conventional 5% level of significance by quoting the actual significance level of the data, rather than merely labelling them 'significant' or 'NS'. To present a confidence interval, though, the confidence level must be preset, and in practice the 95% level of confidence is almost invariably adopted. The magic 5% level of significance is thus reintroduced by the backdoor. This argues against the practice of presenting confidence limits in place of standard errors. The latter permit the reader to calculate her own confidence limits at any desired level of confidence using only the simplest of mental arithmetic.

Confidence limits can be calculated for means, differences between means, variances, regression and correlation coefficients, odds ratios, etc, etc. They are provided by the better statistical computer packages. For details of their calculation, see the BMJ publication *Statistics with Confidence* (1989) edited by M J Gardner and D G Altman. The important issue of the different types of question asked by clinical research workers is discussed at length in *Clinical Trials* by D Schwartz, R Flamant, and J Lellouch (Academic Press, 1980) and more briefly in my article 'Truth and consequences in medical research', *Lancet* 1978;ii:1300–1.

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LETTERS TO THE EDITOR

Providing medical care for children

SIR,—David Hull has produced a masterly overview of the problems facing the medical services for children in this country.[1] Throughout his article he clearly promotes the principles of partnership with parents and cooperation between professionals involved in the care of children which underpin the Children Act 1989. We are therefore concerned that his comments concerning the concept of 'children in need' as found in the Children Act might lead to some misunderstanding among paediatricians. The act states 'a child shall be taken to be in need if: (a) he is unlikely to achieve or maintain . . . a reasonable standard of health or development without the provision for him of services by a local authority, (b) his health or development is likely to be significantly impaired . . . without such services *OR (not and)* (c) he is disabled'.

Thus all disabled children are by definition children in need within the terms of the act, whatever the ability of their parents and entitled to the services provided under part III and schedule 2. All will be eligible for inclusion on the register of disabled children that the local authority will be obliged to set up.

Assessment of all children in need will turn on the child's health, development or disability, and need for services and not on a professional judgment of their parents' abilities, although in many cases they may be a factor. One of the many challenges of the Children Act will be to avoid stigmatisation of families with a child in need who use local authority services. Paediatricians and other child care professionals, if they are effectively to help local authorities identify children in need and encourage the use of services, must have a clear understanding of the concepts within the Children Act. This understanding will also empower professionals in partnership with parents to campaign for the resources local authorities will need if they are to fulfil successfully their obligations under the act to children in need.

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1 Hull D. Providing medical care for children. *Arch Dis Child* 1991;66:643–6.

Life threatening 'epilepsy'

SIR,—In an earlier issue of the journal, Drs Brown and Godman reported a 5 year old girl with spells of unconsciousness which later proved to be caused by ventricular tachycardia and fibrillation.[1] Confusion in diagnosis occurred at first, leading to the presumption of epilepsy as the cause of the 'spells'. This misdiagnosis was based on several medical history items: (i) possible fetal distress preceding the child's birth, (ii) questionable delayed motor development and hypotonia, and (iii) a family history of a cousin with spells caused by ketotic hypoglycaemia.[1] These historical factors suggested that the patient's spells were likely epileptiform. Later complete cardiological evaluation proved that the loss of consciousness was not epileptiform, but rather cardiogenic in origin.

I would like to illustrate further the diagnostic difficulty which can be encountered with long Q-T syndrome in paediatric patients. I cared for an adolescent girl with spells. When she came to see me she had been tentatively diagnosed as having epilepsy and was already receiving phenytoin for that diagnosis. Her spells disappeared during phenytoin treatment. For a variety of reasons I chose to wean and then discontinue the phenytoin. After this had been completed the girl began having more spells of loss of consciousness. At that point I obtained an electrocardiogram (ECG) which demonstrated a long Q-T interval. Holter monitoring confirmed ventricular ectopy, consistent with the diagnosis of long Q-T syndrome.

Presumably phenytoin, a class Ib antiarrhythmic agent *and* an antiepileptic agent, was therapeutic for the patient's problems, despite the fact that the diagnosis under consideration was in error.

The vast number of spells in the paediatric age group are probably benign and due to either breath holding in infancy or situational causes of syncope or epilepsy. Despite this, the relatively rare child with a cardiac conduction defect accounting for her spells certainly exists and *her* spells are certainly life threatening. Their diagnosis often depends on the consultant first seeing them. If the child described above had first seen a paediatric cardiologist, I am quite sure her long Q-T syndrome would have been promptly diagnosed. On the other hand, as a paediatric neurologist first seeing her, I reasonably first considered a diagnosis of seizure disorder.

I do not agree with Garson who in effect states that all new presumed epilepsy patients should have an ECG because of the risk of the spell being of cardiac origin.[2] In fact, I do not think that every new presumed epilepsy patient needs an ECG. Patients presenting with spells are best benefited by the physician thoughtfully considering the broad diagnostic differential of the common paediatric complaint of spells, whether they be due to neurological, cardiological, psychiatric, or metabolic causes.

Neither the patient of Brown and Godman patient nor my patient was harmed by delayed diagnosis. I wish only to add yet one more confounding factor which may possibly be encounted in the care of children with spells.

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Accidents on hospital wards

SIR,—Levene and Bonfield have emphasised the problem of accidents occurring to children on hospital wards and have also demonstrated how information, which previously had been collected solely for medicolegal purposes, could be used for preventative work.[1] A similar case could be made for studying accidents to children in health centres and baby clinics.

By inspecting incident log books maintained by our community unit, it was discovered that for the period 1989–90 inclusive, 17 preschool children in this district were reported as having had accidents while on community health premises.

The commonest reported incident was head injury sustained as a result of a fall; four infants fell from changing mats during weighing sessions and 10 children fell while playing in waiting rooms. Two children had hand injuries due to trapped fingers in swinging doors and one child ingested the boric acid crystals contained in a urine container.

Although none of these incidents resulted in serious injury, the potential for more serious outcome was present. In particular, the importance of injuries to the head as a major cause of childhood mortality and morbidity should be remembered.[2] In retrospect most of the accidents could have been avoided by greater supervision and some modification of clinic premises. In some respects, health centres may be more hazardous to children than hospital wards as they are busy places and supervision of young children is not easy especially in overcrowded waiting rooms. Nevertheless, after our investigation we have endeavoured to increase awareness of child safety among clinic staff and have urged particular caution with regard to the supervision of babies while they are on changing mats.

Child accident prevention should be a key issue for every health authority. By ensuring that children are as safe as is reasonably possible while on health authority premises, we are setting a good example for parents and are ensuring that opportunities for health promotion are not missed.

In addition, it should be remembered that children also have accidents on premises maintained by social services, local education authorities, and borough councils. Perhaps collation of accident data kept by these authorities with appropriate intervention should also form part of every district's child accident prevention strategy.

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1 Levene S, Bonfield G. Accidents on hospital wards. *Arch Dis Child* 1991;66:1047–9.
2 Sharples PM, Storey A, Aynsley-Green A, Eyre JA. Causes of fatal childhood accidents involving head injury in Northern region, 1979–1986. *BMJ* 1990;301:1193–6.

Hazard from the exposed terminals of a battery driven transport incubator

SIR,—In common with most regional intensive care units we offer a retrieval service, collecting about 75 babies annually. Recently an experienced team were collecting an extremely sick baby with pulmonary hypoplasia who required maximal support and monitoring. The baby was transferred to the transport incubator before departure and a pulse oximeter was inadvertently placed on top of the 12 volt car battery used to power the incubator. Sparks and flames ensued, which were extinguished by a quick thinking senior house officer using a carbon dioxide fire extinguisher. The accident would obviously have been much worse if the team had left the hospital.

On close inspection afterwards the metal terminals of the battery were found to be exposed (figure). Current had passed through the casing of the pulse oximeter which still worked. The plastic coverings originally supplied with the battery had long since been mislaid. We report this incident as we feel that other units with old transport systems may also have lost the battery coverings, and suggest that the batteries used to power incubators should be completely encased. Consideration might also be given to inclusion of a fire extinguisher in the flying squad equipment.

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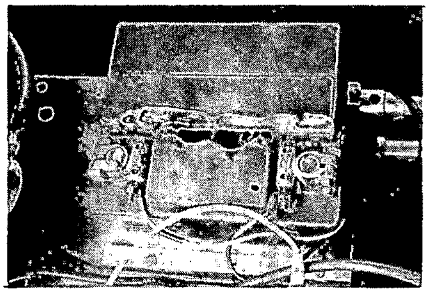

Exposed terminals and damage to battery.

Treating neonatal jaundice with phenobarbitone: the inadvertent administration of significant doses of ethyl alcohol

Sir,—One indication for the administration of phenobarbitone is neonatal jaundice: the drug acts on the immature liver to induce microsomal enzymes and may also have a direct protective effect on the central nervous system.

Phenobarbitone can be given orally as an elixir. The hospital pharmacy will prepare this, on request, as an aqueous solution. In this form, the elixir keeps poorly and cannot be stored on the ward. Stock phenobarbitone elixir on the ward, however, is made with ethyl alcohol to prolong its shelf life. Elixirs in this form are purchased directly from the drug companies and are 40% ethyl alcohol by volume.[1]

Regular dosing with the alcoholic elixir can result in neonatal alcohol toxicity. It should not be taken for granted that the elixir will be aqueous. We would therefore advise that the solvent is also specified on the drug chart when prescribing oral phenobarbitone elixir for neonatal jaundice.

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1 *The EBL guide.* Aylesbury: Edwin Burgess, 1988:178.

Dr Leach comments:
Drs Colquhoun-Flannery and Wheeler are perfectly correct in saying that elixir phenobarbitone contains high amounts of alcohol: the current preparation included in the *British National Formulary* (September 1991) contains 'phenobarbitone 15 mg/5 ml in a suitable flavoured vehicle, containing alcohol 38%'. The current edition of *The Extra Pharmacopoeia* (29th edition, 1989) includes phenobarbitone elixir BP (phenobarbitone oral solution) and states that it is a solution containing phenobarbitone 0·3% and alcohol 38%—that is, the same formulation as the elixir in the *British National Formulary.*

Phenobarbitone has only a low solubility in water (1 in 1000) but is soluble in alcohol (1 in 10). It is therefore necessary to include a high proportion of alcohol in the formulation to achieve adequate solution of the phenobarbitone. An aqueous preparation would require the use of phenobarbitone sodium which is water soluble.

FRANK LEACH
North Western Regional Health Authority,
Regional Drug Information Service

Parenteral lipids and free radicals in preterm infants

Sir,—Professor Cooke describes an interesting association between the use of parenteral lipids and chronic lung disease in preterm infants.[1] The study nicely confirms and extends the results of Hammerman and Aramburo.[2] The author mentions lipid peroxidation and generation of free radicals in the lipid solution as one possible mechanism by which parenteral lipid solutions may injure preterm infants.[1] We should like to draw your readers' attention to the following: free radical induced lipid peroxidation in parenteral lipid solution has actually been described both in vitro and in vivo upon infusion in preterm infants.[3 4] Although the article referred to by the author does not concern lipid peroxidation and free radicals,[5] we agree with Professor Cooke's conclusion that the advantages of parenteral lipid infusion should be carefully weighed against its potential for harm. The possibility of such adverse effects should not be ignored, particularly when using parenteral nutrition in small premature infants. Work with these patients indicates a close association between free radical induced lipid peroxidation and chronic lung disease.[6]

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1 Cooke RWI. Factors associated with chronic lung disease in preterm infants. *Arch Dis Child* 1991;**66**:776–9.
2 Hammerman C, Aramburo MJ. Decreased lipid intake reduces morbidity in sick premature infants. *J Pediatr* 1988;**113**:1083–8.
3 Whispe JR, Bell EF, Roberts RJ. Assessment of lipid peroxidation in newborn infants and rabbits by measurements of expired ethane and pentane: influence of parenteral lipid infusion. *Pediatr Res* 1985;**19**:374–9.
4 Pitkänen O, Hallman M, Andersson S. Generation of free radicals in lipid emulsion used in parenteral nutrition. *Pediatr Res* 1991;**29**:56–9.
5 Pereira GR, Fox WW, Stanley XA, Baker L, Schwartz JG. Decreased oxygenation and hyperlipemia during intravenous fat infusions in premature infants. *Pediatrics* 1980;**66**:26–30.
6 Pitkänen OM, Hallman M, Andersson SM. Correlation of free oxygen radical-induced lipid peroxidation with outcome in very low birth weight infants. *J Pediatr* 1990;**116**:760–4.

Antenatal diagnosis of inborn errors of metabolism

Sir,—The authors of this paper state that they are unaware that prenatal diagnosis has been attempted for hyperlysinaemia.[1] After the diagnosis of a previously affected child such an attempt has been made in a subsequent pregnancy.[2] The presence of an unaffected fetus was demonstrated by normal amniotic fluid amino acid analysis and normal oxidation of lysine by cultured amniotic fluid cells. Thereafter, the parents refused further attempts at antenatal diagnosis and three affected infants were born, the management of whom has been reported in this journal.[3]

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1 Cleary MA, Wraith JE. Antenatal diagnosis of inborn errors of metabolism. *Arch Dis Child* 1991;**66**:816–22.
2 Gray RGF, Bennett MJ, Green A, *et al.* Studies on a case of persistent hyperlysinaemia with a possible method for prenatal diagnosis. *J Inherited Metab Dis* 1983;**6**(suppl 2):115–6.
3 Gregory JW, Beail N, Boyle NA, Dobrowski C, Jackson P. Dietary treatment of hyperlysinaemia. *Arch Dis Child* 1989;**64**:716–20.

Transient gluten intolerance

Sir,—Burgin-Wolff *et al* report that 11% of children (15/134) who were originally diagnosed as having coeliac disease, with a flat small intestinal mucosa and clinical response to a gluten free diet, had a normal small intestinal mucosa after four to 15 years of regular gluten challenge.[1] Thus there had been no histological or clinical relapse after this interval making it possible that the original diagnosis in these children was transient gluten intolerance rather than coeliac disease. None the less Polanco and Larrauri have reported five children with coeliac disease who took up to nine years to relapse after gluten challenge having been shown to have normal small intestinal mucosal biopsies four to five years after gluten challenge.[2] Thus some of the children reported by Burgin-Wolff *et al* may ultimately relapse. Nevertheless it is of great importance that all 15 children who have not relapsed were aged less than 2 years at initial diagnosis. This finding provides firm data to support the revised European Society for Paediatric Gastroenterology and Nutrition (ESPGAN) criteria for coeliac disease[3] recommendation that children originally diagnosed as coeliac disease under the age of 2 years should always have the diagnosis established by means of serial biopsies coupled with gluten elimination and challenge as originally recommended.[4] No child over this age failed to relapse in the study of Burgin-Wolff *et al.*

What still remains unknown is the gamma-delta status of the intraepithelial lymphocytes of biopsy specimens from children diagnosed as having transient gluten intolerance.

T lymphocytes expressing gamma-delta are invariably increased in the gut epithelium in coeliac disease and occasionally in other enteropathies, but only in infancy.[5] It is not possible at present to use monoclonal antibodies for these markers on paraffin sections so old biopsy specimen in paraffin blocks cannot be used. So it will thus take some years to determine this point.

Finally it is disappointing that the authors[1] use the term transient coeliac disease rather than transient gluten intolerance as recommended by ESPGAN since 1970.[4] Coeliac disease, although perhaps expressing itself in different ways in the small intestinal mucosa at different times of life, is by definition a permanent lifetime disorder.

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1 Burgin-Wolff A, Gaze H, Hadziselimovic F, *et al.* Antigliadin and antiendomysium antibody determination for coeliac disease. *Arch Dis Child* 1991;**66:**941–8.
2 Polanco I, Larrauri J. Does transient gluten intolerance exist? In: Kumar J, Walker-Smith JA, eds. *Coeliac disease: 100 years.* Leeds: University of Leeds Printing Service, 1990: 226–8.
3 Walker-Smith JA, Guandalini S, Schmitz J, Schmerling DH, Visakorpi JK. Revised criteria for diagnosis of coeliac disease. *Arch Dis Child* 1990;**65:**909–11.
4 Meeuwisse GW. Diagnostic criteria in coeliac disease. *Acta Paediatr Scand* 1970;**59:**461.
5 Spencer J, Isaacson PG, MacDonald TT, Thomas AJ, Walker-Smith JA. Gamma/delta T cells and the diagnosis of coeliac disease. *Clin Exp Immunol* 1991;**85:**109–13.

Long term survival after heart transplantation for doxorubicin induced cardiomyopathy

Sɪʀ,—We read with interest the case report of the child with severe cardiomyopathy requiring cardiac transplantation after the administration of doxorubicin.[1] We wish to emphasise the increasing problem of anthracycline induced cardiomyopathy not only in the short term, as is the reported patient, but also many years after its use.

Case report

This girl presented at the age of 4·8 years with a Wilms' tumour. She initially underwent laparotomy and removal of the tumour and was found to have stage III disease. Chemotherapy with vincristine, actinomycin D, and doxorubicin (Adriamycin) was commenced. She went on to receive radiotherapy in a dose of 2000 cGy to the renal bed; the field did not include the heart. Chemotherapy was continued with cycles of three weeks for a further 11 months; she received a total dose of 360 mg/m^2 of doxorubicin.

She remained well until December 1990, when at the age of 15·3 years she presented with a three week history of malaise and lethargy with abdominal pain and vomiting. Four days before her admission she developed symptoms of breathlessness, orthopnoea, and weight gain. She was found to have severe congestive cardiac failure confirmed on echocardiography, which also revealed an extensive mural thrombus in the left ventricle.

Despite an initial response to conventional treatment with diuretics and angiotensin converting enzyme inhibitors, her myocardial function remained poor and she underwent orthotopic cardiac transplantation in March 1991. She remains well.

The acute cardiac toxicity of anthracyclines is well recognised with the recent reports of doses as low as 40 mg/m^2 causing some degree of cardiac dysfunction.[2] We are now seeing late toxicity with increasing frequency and it is vital that these children remain on regular follow up, and that there is good liason with adult physicians who also require access to the patient's records and details of chemotherapy received.

With the improved survival of many of the childhood malignancies, it is essential to consider whether the more frequent use of anthracyclines is justified.

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1 Arico M, Pedroni E, Nespoli I, Vigano M, Porta F, Burgio GR. Long term survival after heart transplantation for doxorubicin induced cardiomyopathy. *Arch Dis Child* 1991;**66:** 985–6.
2 Lipshultz S, Colan S, Gelber R, *et al.* Late cardiac effects of daunorubicin therapy for acute lymphoblastic leukaemia in childhood. *N Engl J Med* 1991;**324:**808–15.

Aristotle, Francois Mauriceau, and plagiarism

Sɪʀ,—I write to defend a venerable colleague against the charges of plagiarism raised against him by Professor Dunn in January issue of this journal.[1] I refer, of course, to Francois Mauriceau (1637–1709), who was accused by Professor Dunn of having 'lifted' his recommendation of the dorsal recumbent delivery position from an ancient obstetrical treatise by Aristotle, which was cited in an 18th century translation called *Aristotle's Experienced Midwife.*

There are, however, no genuine extant obstetrical treatises written by Aristotle. On the contrary, towards the end of the 17th century there began to appear a number of anonymous medical and sexual 'self help' books or 'marriage manuals' attributed to Aristotle. They were reprinted extensively throughout the 18th and 19th centuries and even into the 20th century. While they have their roots in medieval and renaissance lore, they freely plagiarised from 'contemporary' medical works at the time in which they were written. Among the most notable of these works are *Aristotle's Compleat Masterpiece in Three Parts, Displaying the Secrets of Nature in the Generation of Man; Aristotle's Book of Problems . . . Touching the State of Man's Body; Aristotle's Last Legacy Unfolding the Mysteries of Nature in the Generation of Man;* and Professor Dunn's 'Aristotlelian' treatise, *Aristotle's Compleat and Experienc'd Midwife.*[2] This source dates from the mid-18th century and was published well after Hugh Chamberlen's English translation of Mauriceau's work on obstetrics in 1673.

The similarities in style are best explained by the anonymous 'Aristotle' lifting *his* text from Chamberlen's translation of Mauriceau, *not* the other way around. Rather than being the culprit, Mauriceau is the victim in this instance. Professor Dunn owes him an apology!

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1 Dunn PM. Francois Mariceau (1637–1709) and maternal posture for parturition. *Arch Dis Child* 1991;**66:**78–9.
2 Bouce PG. Some sexual beliefs and myths in eighteenth-century Britain. In: Bouce PG, ed. *Sexuality in eighteenth-century Britain.* Manchester: Manchester University Press, 1982:28–46.

Professor Dunn comments:

Plagiarism, or the passing off of the ideas of another as one's own, is something we all do to a greater or lesser extent. As Wilson Mizher has pointed out: 'If you steal from one person it's plagiarism; if you steal from many, it's research'! Dr Wall's speculation that Mauriceau was himself plagiarised by the anonymous 18th century author or editor of *Aristotle's Compleat and Experience Midwife,* rather than that he plagiarised Aristotle as I suggested in my article, is of considerable interest. If he is correct, as he may well be, then I certainly owe Mauriceau an apology. Even more so I would need to apologise to the reputation of Aristotle for incorrectly asserting that he, alone among the classical workers, had advocated that women adopt the unphysiological dorsal position for delivery. If I were Dr Wall's 'venerable colleague' I would much prefer to be found guilty of plagiarism than of being responsible for introducing into Western obstetrics a practice which has made childbirth more painful, more difficult, and more dangerous for both mother and child.

BOOK REVIEWS

Yearbook of Pediatrics 1991. Edited by F A Oski and J A Stockman (editor in chief Nancy Gorham). (Pp 528; £39 hardback.) Mosby Year Book, 1991. ISBN 0–8151–6586–2.

I recall my senior consultant physician informing me wearily, but proudly, that he kept up to date by reading Price's *Textbook of Medicine* from cover to cover every year. We paediatricians are more fortunate. The *Yearbook of Pediatrics* provides an annual review of the world's literature and is liberally seasoned with commentaries that are both readable and memorable. The Yearbook aims to comment on the important issues in paediatrics and contains 19 chapters covering all the system specialities as well as ophthalmology, dentistry, otolaryngology, therapeutics, toxicology, and adolescent medicine as well as an interesting miscellaneous section. Topics range from bedtime cereal to Behçet's disease, and from liver transplantation to Lyme disease.

A total of 280 articles from over 100 journals are abstracted together with one or two tables or figures where appropriate. Each is accompanied by a commentary written either by one of the editors, Frank A Oski and James A Stockman, or by an invited expert. They vary from brief, witty, and sometimes caustic comments to sound commonsense based on broad practical experience. Often controversial, sometimes irreverent, and on occasions deliberately irrelevant, they provide both a valuable *aide memoire* and a stimulus to read on.

Inevitably a book of this size cannot cover the whole of paediatrics comprehensively, but the range is impressive and serious omissions few. Surprisingly there are only two abstracts on AIDS and one on sexual abuse, presumably both have been well covered in previous years.

The Yearbook has both a subject and author index with useful cross references between chapters and to previous editions; however this is not a reference book and should not be consigned to the library shelf. It is a book to be read at leisure, chapter by chapter, by all paediatricians whatever their specialty and will delight all who remain general paediatricians at heart.

Sadly for those who have admired Oski's editorship and commentaries over the last 13 years, this is his last volume. His quotes and misquotes do much to enrich the book. 'Even if you are on the right track, you will get run over if you just sit there', 'pesky pestiviruses', and 'smoking is one of the leading causes of statistics', are some of my favourite quotes from this edition. He has yet to find the meaning of the Chinese proverb 'when walking through a melon patch, don't adjust your sandals—any offers?

KEITH DODD
Consultant paediatrician

Diagnostic Dysmorphology. Jon M Aase. (Pp 299; $49·50 hardback.) Plenum Medical Book Company, 1990. ISBN 0–306–43444–X.

Upon reading this book I discovered to my great relief that most of my 'personal' congenital abnormalities and those of my children are indeed all part of normal variation and have no other sinister significance. Dysmorphology is commonly thought to be a subject studied only by those with a fascination for small print and a memory for long names. With no formal training programme, it remains a mysterious question as to how one can actually acquire skills as a dysmorphologist. Based on the analogy of Sherlock Holmes solving a mystery, this book offers an excellent introduction to dysmorphology with a clinical approach to the identification of dysmorphic features.

An overall summary of the scope of dysmorphology is followed by a useful guide to the history and examination of the dysmorphic patient. Each anatomical region is then covered in turn, dealing with embryological development, anatomic relations, examination techniques, minor variants, and abnormalities. It is good to see that behavioural features are not missed out as an important clue to dysmorphological diagnosis. Strategies for arriving at a final diagnosis are discussed, with emphasis being placed on the 'Sherlock Holmes' method. This approach takes into account the 'intuitive' aspect of dysmorphology as well as the more methodical sifting of signs and symptoms and emphasises that a combination of the two is probably the best answer. It would have been useful to include a couple of cases which had been worked through according to this approach to demonstrate the final step of seeking the specific diagnosis.

This book is intended only to instruct one on how to choose the correct diagnostic area. It is not a compendium of differential diagnoses and does not contain any information on cytogenetics, molecular genetics, or other laboratory data. There are ample black and white figures throughout, although not all are of good quality. The reference section provides a comprehensive list of catalogues and computer programs to consult thereafter.

In this book Jon Aase examines dysmorphological diagnosis from a wide viewpoint, considering the social and emotional issues involved in affixing a diagnostic label as well as the clinical features. It teaches us to seek not just a name for a condition but to ask ourselves why it happened, and shows that with logical thinking and careful attention to detail, most clinicians can learn to recognise dysmorphic features from normal ones, and more importantly, guard against the inappropriate 'labelling' of a child and the consequences thereof.

Like all good detective stories, I couldn't help reading this book right through once started. It would make excellent reading for all those involved in the care of the normal newborn, as well as general and community paediatricians. Those already experienced in dysmorphology will also learn something new and it is a 'must' for those among us who have always wondered why an umbilicus looks the way it does!

JILL CLAYTON-SMITH
Clinical research fellow

Adult and Pediatric Urology. 2nd Ed. Vol 1 and 2. Edited by J Gillenwater, J Grayhack, S Howards, and J Duckett. (Pp 2366; £189 hardback.) Mosby Year Book, 1991. ISBN 0–8151–3549–9.

Adult and Pediatric Urology, a two volume boxed set, totalling nearly 2500 pages is hardly light reading. The paediatric section alone represents the equivalent of a substantial textbook. For the average American paediatric urologist, this format makes good sense, as most train initially as adult urologists and maintain close links with the specialty. Elsewhere in the world the potential purchaser is likely to be deterred by the weighty coverage of adult urology, which is a pity as the paediatric section represents the most up to date and authoritative account of the specialty currently available.

The first 100 pages reflect the new face of paediatric urology—prenatal diagnosis. A brief introductory consideration of genetics leads into a lengthy but readable account of perinatal urology including fetal intervention. The bread and butter of paediatric urology: hydronephrosis, obstruction, reflux, and hypospadias, is well served by clearly written chapters which cover embryology, diagnosis, and surgical management.

Singling out individual chapters is difficult as the overall standard is consistently high. Snyder's chapter on the principles of paediatric urinary reconstruction is a *tour de force* which encompasses the many innovations in this exciting field. The contributions on paediatric urological oncology and renal transplantation in childhood are excellent, having been co-authored by internationally acknowledged experts in their respective fields. Less successful are the chapters on the undescended testis. Perhaps this is not surprising given the diversity of opinion on the subject and the paucity of hard facts. Reviewing his extensive experience of testicular histopathology, Hadziselimovic puts forward the case for hormone treatment. A case which is then immediately refuted in the next chapter entitled 'An additional viewpoint'. Second thoughts on the part of the editors? A number of studies have confirmed the superiority of laparoscopy for locating an impalpable testis but surprisingly the technique receives no mention.

These criticisms apart, the paediatric section is difficult to fault. Judged in its own right it would make an excellent textbook. For paediatric urologists and surgeons outside the United States the publishers should perhaps consider binding and marketing the paediatric section as a separate volume.

DAVID F M THOMAS
Consultant paediatric urologist/surgeon

MEETINGS IN 1992

The Neonatal Society
20 February, Royal Society of Medicine, London
Further details: Dr Andrew Wilkinson, Neonatal Unit, Department of Paediatrics, John Radcliffe Maternity Hospital, Headington, Oxford OX3 9DU

Clinical Genetics Society
18 March, London
23–25 September, Nottingham
Further details: Dr Peter Farndon, Clinical Genetics Unit, Birmingham Maternity Hospital, Edgbaston, Birmingham B15 2TG

Paediatric Research Society
27–28 March, Newcastle upon Tyne
September/October (dates undecided), Galway, Ireland
Further details: Dr L T Weaver, MRC Dunn Nutrition Unit, Milton Road, Cambridge CB4 1XJ

British Paediatric Association
7–10 April, University of Warwick, Coventry
Further details: Miss Rosalind Topping, British Paediatric Association, 5 St Andrew's Place, Regents Park, London NW1 4LB

Ambulatory Pediatric Association
4–8 May, Baltimore
Further details: Marge Degnon, Ambulatory Pediatric Association, 6728 Old McLean Village, McLean, VA 22101, USA

European Society for Paediatric Gastroenterology and Nutrition
27–30 May, Brussels
Further details: Dr Isabelle Polanco, Hospital de la Paz, PO Castallena 261, Madrid 28046, Spain

European Society for Pediatric Research
14–17 June, Uppsala
Further details: Professor Gunnar Sedin, Department of Pediatrics and Perinatal Research Laboratory, University Hospital, S-751 85, Uppsala, Sweden

European Respiratory Society Pediatric Assembly
29 August–3 September, Vienna
Further details: Professor M Zach, University Kinderklinik, Graz, Austria

The 5th Congress of the International Perinatal Doppler Society
30 August–2 September, New York
Further details: Dr Harold Schulman, Department of Obstetrics and Gynecology, Winthrop University Hospital, 259 First Street, Mineola, New York 11501–3932, USA

European Society for Paediatric Endocrinology
6–9 September, Zaragoza, Spain
Further details: Dr Angel Ferrandez-Longa, Hospital Insantil, 'Miguel Servet', Paseo Isabel la Catolica 1, 50009 Zaragoza, Spain

International Congress of Pediatrics
6–10 September, Rio de Janiero
Further details: Secretariat, Gentry, Rua Visconde de Ouro Preto, 37-Sala 102, CEP 22250, Rio de Janiero, Brazil

British Association of Perinatal Medicine
12 September, Sheffield
Further details: Dr Richard G Pearse, The Jessop Hospital for Women, Leavygreave Road, Sheffield S3 7RE

Archives of Disease in Childhood 1992; **67**: 156

INSTRUCTIONS TO AUTHORS

Papers for publication should be sent to the Editors, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR. Submission of a paper will be held to imply that it contains original work not being offered elsewhere or published previously. Manuscripts should be prepared in accordance with the Vancouver style.[1] The editors retain the right to shorten the article or make changes to conform with style and to improve clarity.

For guidance on ethical aspects refer to the editorial in this journal.[2] All authors must sign the copyright form after acceptance.

Failure to adhere to any of these instructions may result in delay in processing the manuscript and it may be returned to the authors for correction before being submitted to a referee.

General

- Authors must submit two copies of the manuscript and any subsequent revision.
- When submitting original manuscripts authors should send a copy of any of their other papers on a similar subject to assure the editors that there is no risk of duplicate publication.
- Manuscripts must have a title page which gives the title of the paper, the name of the author(s), the place where the work was carried out, and the address of the corresponding author. The authors should include their family names and initials. The number of authors should be kept to a minimum and should include only those who have made a contribution to the research: justification should be made for more than five authors. Acknowledgments should be limited to workers whose courtesy or assistance has extended beyond their paid work, and to supporting organisations. Information about the availability of reprints should be given at the end of the references.
- The article and references must be typed in double line spacing throughout (including tables) with margins of at least 2·5 cm. The right hand margin should not be justified. Pages should be numbered in the top right hand corner.
- All measurements must be in SI units apart from blood pressure measurements, which should be in mm Hg and drugs in metric units.
- Abbreviations should be used rarely and should be preceded by the words in full before the first appearance.
- In the statistical analysis of data 95% confidence intervals should be used where appropriate.
- Any article may be submitted to outside peer review and for statistical assessment. This may take up to six weeks. Articles are usually published within five months of the date of the final acceptance of the manuscript.
- No free reprints will be provided. Reprints may be ordered when the proof is returned; they take about two months to be dispatched and those going overseas are sent by surface mail.
- If the paper is rejected the manuscript and all illustrations will be shredded unless a request is made at the time of submission for return of the illustrations.

Original articles

- The title should have no more than 10 words and should not include the words 'child', 'children', or 'childhood' (already implicit in the title of the journal).
- The abstract of an experimental or observational study must clearly state in sequence and in not more than 150 words (i) the main purpose of the study, (ii) the essential elements of the design of the study, (iii) the most important results illustrated by numerical data but not p values, and (iv) the implications and relevance of the results. The abstract of a paper which focuses on a case report(s) must summarise the essential descriptive elements of the case(s) and indicate their relevance and importance.

Short reports

- Length must not exceed 900 words, including an abstract of less than 50 words, one or two small tables or illustrations and up to six references. If more illustrations are required the text must be reduced accordingly.
- The title should be no longer than seven words.

Annotations

- Annotations are commissioned by the editors who welcome suggestions for topics or authors.

Letters

- Letters must be typed in double line spacing, should normally be no more than 300 words, have no more than four references, and must be signed by all authors. Two copies should be provided. Letters may be published in a shortened form at the discretion of the editor.

Tables and illustrations

Tables should be presented separately and typed in double line spacing without ruled lines.

- Avoid histograms if possible.
- Illustrations should be used only when data cannot be expressed clearly in any other way. When graphs are submitted the numerical data on which they are based should be supplied.
- Illustrations should be trimmed to remove all redundant areas; the top should be marked on the back.
- Patients shown in photographs should have their identity concealed or written consent to publication should be obtained.
- Ultrasound scans or other pictures should be arrowed on an overlay to indicate areas of interest or should be accompanied by explanatory line drawings.
- If any tables or illustrations submitted have been published elsewhere, written consent to republication should be obtained by the author from the copyright holder (usually the publisher) and the authors. A copy of the letter giving consent must be included.

References

- References must be numbered in the order they appear in the text and include all information (Vancouver style):

  1 Williams W, Sunderland R. As sick as a pigeon—psittacosis myelitis. *Arch Dis Child* 1989;**64**:1626–8.

  2 Hughes CA. Parenteral nutrition. In: Insley J, Wood B, eds. *A paediatric vade mecum*. London: Lloyd-Luke, 1984:60–7.

- Please note that in the new Vancouver style (4th edition, 1991) all authors must be given but if the number exceeds six give six names followed by *et al* (instead of three).[1]
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Annotations

Antibiotic choices for meningitis beyond the neonatal period

In the past decade a variety of new antibiotics have become available that are both highly active against the common meningeal pathogens and that also achieve excellent bactericidal concentrations in the cerebrospinal fluid. There is now an extensive literature documenting the effectiveness of these agents in treating bacterial meningitis. The purpose of this review is to consider the evidence in favour of using the newer antibiotics in preference to more conventional treatment regimens.[1]

In order to select the optimal antibiotics for the initial treatment of bacterial meningitis, consideration must be given to the following factors: the spectrum of pathogens causing meningitis in different age groups, the changing pattern of antimicrobial resistance, the pharmacological properties of the antibiotics available, and the results of therapeutic trials.

The organisms most commonly responsible for causing bacterial meningitis vary significantly with the age of the patient. The optimal antibiotic regimen will therefore be different for neonates, young infants, and older children. In the neonatal period, *Escherichia coli* and other Gram negative bacilli, group B streptococcus, and *Listeria monocytogenes* are the important meningeal pathogens. In children older than 3 months nearly all cases of community acquired meningitis are caused by *Neisseria meningitidis, Streptococcus pneumoniae,* or *Haemophilus influenzae,* the latter organism predominantly infecting children younger than 6 years. Infants between 1 and 3 months of age may be affected by either the neonatal or the childhood spectrum of pathogens.[2]

A major determinant of antibiotic choice in the treatment of bacterial meningitis is the continually changing pattern of antibiotic resistance. When ampicillin was first introduced into clinical practice, all strains of *H influenzae* were fully sensitive to it. Since then, however, there has been a progressive increase in resistance to this antibiotic and currently at least 15% of *H influenzae* isolates causing invasive disease in the UK are resistant to ampicillin.[3 4] It is disturbing that in some countries, such as the USA, resistance is now as high as 30%. In the light of this, ampicillin can no longer be recommended as the sole agent for the initial treatment of meningitis in children less than 6 years of age.[5 6] Although most strains of *H influenzae* remain sensitive to chloramphenicol, resistance is now found in up to 3% of invasive isolates in England and Wales.[3] Moreover, many of these strains are now also resistant to ampicillin,[3 4 7] and in Spain resistance to both drugs is increasing.[8]

Though resistance of *H influenzae* to conventional antibiotics is of primary concern, there are an increasing number of disturbing reports that antibiotic resistance is developing to other meningeal pathogens. Penicillin resistant pneumococci are still uncommon in the UK, but have become more prevalent in many countries including Spain and South Africa.[9 10] These strains have altered penicillin binding proteins and are only inhibited by relatively high concentrations of the antibiotic. Penicillin insensitive strains of pneumococci currently remain sensitive to the newer cephalosporins.[9 10] Penicillin resistant meningococci are also emerging as a problem in Spain and South Africa.[11 12] Fortunately most strains in the UK are still fully sensitive to penicillin but insensitive isolates are now being recognised and it is likely that meningococcal resistance will be an important factor influencing antibiotic selection in the future.[13]

The ideal antibiotic for the treatment of meningitis should not only have activity against the expected pathogens, but must also penetrate into the cerebrospinal fluid in sufficient concentrations to achieve several times the minimum bactericidal concentration of the infecting organism. In addition it should be cheap, free from side effects, and have a high therapeutic to toxicity ratio.

Chloramphenicol penetrates well into the cerebrospinal fluid in the presence or absence of meningeal inflammation, achieving concentrations of 65% of that found in the plasma, and considerably in excess of the inhibitory concentrations for sensitive pathogens. Chloramphenicol is bactericidal for *H influenzae, N meningitidis,* and *S pneumoniae,* and when administered orally, achieves similar blood and cerebrospinal fluid concentrations to those obtained by intravenous administration. This property is unique among the agents used to treat meningitis and makes chloramphenicol the only antibiotic that is effective when administered orally. Although chloramphenicol has been the mainstay of treatment for meningitis beyond the neonatal period for many years, the emergence of chloramphenicol resistant *H influenzae,* and the potential for marrow toxicity are drawbacks to its use. In addition variable metabolism of the drug in children with shock or liver dysfunction, and the necessity to monitor serum concentrations both to prevent dose dependent toxicity and to prevent inadequate therapeutic concentrations, are further disadvantages.[14]

β Lactam antibiotics do not penetrate well into the cerebrospinal fluid in healthy individuals, but in the presence of meningeal inflammation adequate cerebrospinal fluid concentrations are achieved to inhibit sensitive strains.

The exceptional safety record of the penicillins, and their high therapeutic to toxic ratio, have made penicillin the drug of choice for treating meningococcal and pneumococcal meningitis, and ampicillin is still an excellent drug for treating sensitive strains of *H influenzae*.

The first generation cephalosporins proved unreliable for the treatment of meningitis. However, cefuroxime, a second generation cephalosporin active against *H influenzae, S pneumoniae*, and *N meningitidis*, penetrates well into the cerebrospinal fluid and has proved effective as a single agent for initial treatment of childhood meningitis.[15 16] Cefuroxime has been used extensively in both Europe and the USA as a single agent for treatment of meningitis. However, several reports have suggested that both sterilisation of the cerebrospinal fluid and clinical outcome may be inferior to that achieved with the newer third generation cephalosporins.[16–18]

The third generation cephalosporins cefotaxime, ceftazidime, and ceftriaxone have greatly enhanced the armamentarium against both the neonatal and childhood meningeal pathogens.[18–22] All three agents are extremely active against *S pneumoniae, H influenzae* (including β lactamase producing strains) and *N meningitidis* and achieve cerebrospinal fluid concentrations greatly in excess of their minimum bactericidal concentrations. The third generation cephalosporins are also extremely safe and monitoring of serum concentrations is not required. Side effects are rare and are similar to those of the penicillins, including skin reactions, gastrointestinal upset, and neutropenia. Ceftriaxone is the most potent of the new cephalosporins. It has a long plasma half life, and can therefore be administered on a once daily basis.[23 24] However gastrointestinal side effects are more common with ceftriaxone, and bile sludging detected by ultrasound is frequently observed, but is probably not clinically significant.[1 18 21]

The paediatric and infectious disease literature published over the past few years contains a number of reports of open and comparative trials assessing the use of the new cephalosporins and conventional antibiotic regimens in meningitis. For those hoping that the newer drugs would provide the 'magic bullet' which would reduce the mortality and long term morbidity from meningitis, these trials are disappointing. Cefuroxime, ceftazidime, cefotaxime, and ceftriaxone have all proved effective in treating meningitis, but despite reports that they achieve sterilisation of the cerebrospinal fluid more rapidly than ampicillin and chloramphenicol,[22] mortality rates and neurological sequelae have not been significantly improved. From the studies published to date it can be concluded that single drug treatment with cefuroxime or the third generation cephalosporins is as effective but not necessarily better than the standard combination of ampicillin or penicillin and chloramphenicol.

The apparent lack of evidence that the cephalosporins are superior to ampicillin or chloramphenicol, despite their greater in vitro activity, must be interpreted with caution. In order for comparative trials of these antibiotics to show significant differences in mortality or neurological sequelae, hundreds of patients would need to be included in each arm of a trial. Such trials are always very difficult and costly to undertake. All the published studies have contained relatively small numbers of patients and differences in mortality would not necessarily have been detected.

If the cephalosporins are to be used for initial treatment of meningitis in preference to ampicillin and chloramphenicol it is necessary to consider which of these drugs should be recommended.[1] There have been few trials directly comparing all of these antibiotics. In studies published to date, ceftriaxone has resulted in more rapid sterilisation of the cerebrospinal fluid than either cefotaxime or cefuroxime.[17 18 22] Furthermore in one study the incidence of deafness was reduced in ceftriaxone treated patients compared with those treated with cefuroxime.[18] The evidence is therefore accumulating that the third generation cephalosporins, particularly ceftriaxone, are more effective for the treatment of bacterial meningitis than cefuroxime. Ceftazidime is less active against pneumococci than cefotaxime and should be reserved for pseudomonal infections.

Recommended antibiotics for initial treatment of meningitis in different age groups

Age group	*Drug*	*Dose/day*
Infants 1 month to 3 months	Ampicillin and cefotaxime	200 mg/kg 200 mg/kg
Older infants and children	(1) Cefotaxime or ceftriaxone (2) Ampicillin and chloramphenicol*	200 mg/kg 100 mg/kg 200 mg/kg 75–100 mg/kg

*Measurement of therapeutic concentrations of chloramphenicol is necessary.

Current recommendations

Our current recommendations for initial antibiotic treatment of bacterial meningitis are shown in the table. In infants between 1 and 3 months of age a combination of ampicillin and cefotaxime is a logical choice as cefotaxime provides cover for both neonatal and infant pathogens and ampicillin is effective against *L monocytogenes*.

For older infants and children we recommend a third generation cephalosporin (cefotaxime or ceftriaxone) in preference to the combination of penicillin or ampicillin and chloramphenicol. Although the mortality and long term morbidity of patients treated with the newer antibiotics is similar to those treated with conventional therapy, our decision is based upon (1) the lack of toxicity of the third generation cephalosporins, (2) the emerging resistance of the three major pathogens to conventional treatment, (3) the elimination of the need to monitor serum concentrations, and (4) the convenience and reliability of using a single agent which can be administered on a one to three times daily basis. Although the cephalosporins are more expensive than penicillin or ampicillin and chloramphenicol, when the nursing cost of administering two drugs every six hours are compared with those of giving a single agent one to three times daily, the total costs are fairly similar.

Once the causative organism has been identified, and the antibiotic sensitivities determined, intravenous penicillin can be substituted for treating sensitive meningococcal and pneumococcal infections. In cases of meningitis where the identity or the sensitivity of the causative organism cannot be definitively determined, we would continue to use a third generation cephalosporin.

Traditionally *H influenzae* or *S penumoniae* meningitis have been treated for 10 to 14 days, and meningococcal meningitis for seven days.[25] Several recent studies have indicated that seven days of treatment is probably adequate for all three childhood pathogens, but the numbers of patients treated with the abbreviated course are too small to make definite recommendations.[25] We currently recommended seven days treatment for *N meningitidis* and 10 days for *H influenzae* and *S pneumoniae* meningitis.

Conclusion

There is now a range of antibiotics that are effective in treating bacterial meningitis. Although the results of trials have not as yet indicated that the mortality and morbidity is improved by the third generation cephalosporins, they offer advantages in terms of ease of administration, safety, and lack of resistance. With an increasing array of new agents becoming available, paediatricians will have to continually re-evaluate antibiotic policies as patterns of microbial resistance change and new drugs enter clinical use. It is unlikely however that new antibiotics alone will significantly alter the mortality and morbidity associated with bacterial meningitis. The advent of effective vaccines and new therapeutic interventions to modulate the damaging host inflammatory response to invading micro-organisms should ultimately improve the outcome of bacterial meningitis in the future.

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Fibreoptic bronchoscopy in infants

In the past decade endoscopic airway examination has become an important diagnostic tool.[1] In neonates and infants the aims of fibreoptic bronchoscopy are nearly the same as in older children: assessment of proximal airway patency and sampling of lavage fluids for microbiological, cytological, or chemical studies. There are a number of special problems in infants: frequency of malformations and malacias, and mechanical complications of assisted ventilation. As the fibreoptic bronchoscopes are obstructive, the smallest infants and those with precarious respiratory status demand well trained operators and well adapted techniques and instruments. These precautions should allow exploration of infants' airways safely and lead to subsequent investigations and the diagnosis.

Techniques

Despite some uncertainty as to the indications for rigid bronchoscopes and fibreoptic bronchoscopes, paediatricians generally prefer fibreoptic bronchoscopes for most procedures.[2] The standard paediatric fibreoptic bronchoscopes have an external diameter of 3·5 mm and an operating channel of 1·2 mm (Olympus BF 3C20, FB 10-H Pentax). Most examinations can be performed with sedation and local anaesthesia.[3,4] The flexibility of the bronchoscope increases the patient's comfort. The controlled angulation of the distal tip allows more selective manoeuvres and improves the visualisation of the upper lobe bronchi. Fewer medical and nursing personnel are required with fibreoptic bronchoscopy. It can be performed on an outpatient basis and even at the bedside of the infants in intensive care units. Rigid bronchoscopes are more suitable for the removal of foreign bodies, excision of granulation tissue, and examination of tracheo-oesophageal fistulas.[3,5] Their internal diameter allows the insertion of forceps for bronchial biopsies. Clearly rigid and flexible bronchoscopes neither duplicate nor replace each other, rather they are complementary and should be used when appropriate for the particular problem.

When fibreoptic bronchoscopy is indicated, it must be carried out in a properly equipped and staffed room with facilities for resuscitation. In our practice sedation is achieved with subcutaneous atropine 0·01 mg/kg and rectal midazolam 0·25 mg/kg between 6 months and 1 year and 0·5 mg/kg between 1 and 2 years. Infants younger than 6 months are given atropine and rectal diazepam 0·5 mg/kg.

As the fibreoptic bronchoscope is passed through the nose, careful topical anaesthesia of upper airways and larynx is an important step. For a skilled operator, the duration of fibreoptic bronchoscopy does not exceed 2–3 minutes. Oximetry and electrocardiographic monitoring are mandatory in infants with low weights or borderline respiratory status. Supplemental oxygen through the free nostril is indicated in infants less than 5 kg, in children with diffuse lung disease, and in children with borderline or poor blood gases. The fibreoptic bronchoscope is reinserted several times if necessary.

Anatomical indications

Bronchoscopy is required to diagnose anatomical abnormalities responsible for persistent or recurrent pneumonia, atelectasis, or hyperinflation. Specific laryngeal problems have been reviewed elsewhere by ear, nose, and throat specialists.[6]

Fibreoptic bronchoscopy is particularly indicated in an infant with persistent wheezing or inspiratory and expiratory stridor, chronic tracheobronchial hypersecretion that is unresponsive to bronchodilator treatment, physiotherapy and antibiotics, and particularly if chest radiography is abnormal. Fibreoptic bronchoscopy frequently yields significant abnormalities of the lower respiratory tract such as unsuspected foreign bodies, tracheal stenosis, endobronchial masses, bronchial stenosis (especially in infants having previously received prolonged mechanical ventilation), airway compression by aberrant vessels or extrinsic masses, tracheomalacia, and bronchomalacia.[4 7] Only local anaesthesia with spontaneous ventilation permits the study of the dynamic aspects of the airways and the evidence of excessive and premature expiratory collapse of the trachea and the main stem bronchi. Bronchial brushing can be performed with the paediatric fibreoptic bronchoscopy and may confirm the diagnosis of primary ciliary dyskinesia.[8]

In infants with abnormal chest radiography due to pulmonary tuberculosis, fibreoptic bronchoscopy verifies the underlying cause of atelectasis or hyperaeration (compression, granuloma, obstructive cellular debris), indicates resection of granulation tissue by rigid bronchoscopy, or indicates the need for corticosteroids.[9]

Only suspected foreign body aspirations are considered for fibreoptic bronchoscopy. Rigid bronchoscopy with general anaesthesia is required when a foreign body is disclosed by fibreoptic bronchoscopy or when clinical history and radiological findings are highly suggestive of aspiration.

Bronchoalveolar lavage

The aim of fibreoptic bronchoscopy is not limited to anatomical examination of the airways. Obtaining samples for further examination is often required. In an immunocompetent infant, bronchoalveolar lavage (BAL) is used in the investigation of a non-infectious interstitial pneumonitis (pulmonary alveolar proteinosis, haemosiderosis, histiocytosis X). In the immunocompromised infant with interstitial pneumonitis and acute severe pneumonia, BAL is valuable in the diagnosis of an opportunistic infection. The increasing number of patients undergoing immunosuppressive agents for malignancy or for transplantation, and of HIV infected patients, explain the expansion of BAL. In our series of 73 patients where BAL was used for pulmonary infiltrates, 54% of children were less than 2 years of age. BAL disclosed an infectious agent in 50% of cases.[10] The best microbiological yield (75%) was observed in HIV infected children with acute interstitial pneumonitis, mainly *Pneumocystis carinii*. Examination of sputum obtained by non-invasive methods has been advocated in HIV infected children with acute *P carinii* pneumonia.[11 12] The reliability of these methods has been questioned.[12] In chronic interstitial pneumonitis, with clinical and radiological features suggesting pulmonary lymphoid hyperplasia-lymphoid interstitial pneumonitis, BAL showed a characteristic profile associating an isolated lymphocytosis, without neutrophilia or *P carinii*.[13]

Therapeutic bronchoscopy

Atelectasis is frequently observed in infants after extubation or after thoracic surgery. Only the few cases of atelectasis which persist a few days despite chest physiotherapy require fibreoptic bronchoscopy, which can be performed at the bedside. Removal of mucous plugs, or sometimes instillation and reaspiration of normal saline in the atelectatic airway, allows reaeration and improvement of respiratory status.

Fibreoptic bronchoscopy in the neonatal intensive care unit

In infants less than 3000 g, the 3·5 mm fibreoptic bronchoscope will nearly totally obstruct the airway. Preoxygenation with 100% oxygen is mandatory, it provides adequate oxygenation but not ventilation.[14] Despite the possibility of alternatively ventilating or aspirating the airways, the bronchoscope must not remain below the glottis more than 30–40 seconds.[15] The ultrathin fibreoptic bronchoscope now available (outer diameter 2·2 mm) can be passed through a connector located between the endotracheal tube and the ventilator. This connector allows uninterrupted mechanical ventilation and oxygen delivery during the examination.[16 17] This ultrathin bronchoscope has a directional tip, but lacks a suction channel, therefore careful airway suctioning before the procedure is mandatory.

Airway obstruction is a concern particularly, but not exclusively, in newborns and infants receiving mechanical ventilation. Inflammatory stenosis, granuloma, severe extrinsic compression and tracheomalacia or bronchomalacia are frequently observed in infants with persistent radiological abnormalities.[16 18–20] These abnormalities can coexist and their correct diagnosis influences management. Airway compression in congenital cardiopathies may hasten the need for surgery. Inflammatory stenosis and granuloma necessitate extreme care in suctioning to avoid aspirating beyond the endotracheal tube. These conditions might lead to steroid treatment. Positive end expiratory pressure may be required for severe tracheomalacia responsible for sudden 'unexplained' deterioration of respiratory status.[21 22]

Complications of fibreoptic bronchoscopy

Patients with pulmonary hypertension are at high risk and bronchoscopy should be delayed unless the obtained information is considered essential for proper management. At high risk are also infants with severe coagulopathy, although thrombopenia can be corrected for the duration of the procedure. In infants with severe airway obstruction or severe hypoxaemia, fibreoptic bronchoscopy may induce respiratory failure due to the procedure, the BAL, or the sedation. If information gained by fibreoptic bronchoscopy is considered essential, then it should be performed by a highly experienced bronchoscopist in the intensive care unit. Midazolam produces more respiratory depression in the younger infants. This explains why infants between 6 months and 1 year of age are given a half dose and why midazolam is avoided below 6 months. Another reason for withdrawing midazolam is the observation of few cases of brief convulsions in the youngest subgroup (unpublished data). However the role of midazolam alone, compared with midazolam with topical lignocaine, remains undetermined. A transient fever occurs four to six hours after the BAL in 40% of infants and subsides spontaneously.

Conclusions

Bronchoscopy is an essential step in the investigation of numerous neonates and infants with severe or persistent pulmonary disease. The good tolerance and the high diagnostic yield of fibreoptic bronchoscopy have transformed the diagnostic strategy. In the near future the use of this technique in infants will probably expand further. The reduced external diameter of ultrathin bronchoscopes will allow a more comfortable procedure in non-ventilated small infants requiring anatomical evaluation of their airways.

And finally, a better examination of lavage fluid and cells will provide important information about the pathophysiology of lung diseases.[23]

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ORIGINAL ARTICLES

Fourteen cases of imposed upper airway obstruction

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Abstract

Imposed upper airway obstruction was diagnosed as the cause of recurrent and severe cyanotic episodes in 14 patients. Episodes started between 0·8 and 33 months of age (median 1·4) and occurred over a period of 0·8 to 20 months (median 3·5). Diagnosis was made by covert video surveillance, instituted after either (a) the observation that episodes *began* only in the presence of one person, or (b) characteristic findings on physiological recordings, lasting between 12 hours and three weeks, performed in hospital or at home.

Surveillance was undertaken for between 15 minutes and 12 days (median 24 hours) and resulted in safety for the patient and psychiatric assessment of the parent: mother (n=12), father (n=1), and grandmother (n=1). These revealed histories of sexual, physical, or emotional abuse (n=11), self harm (n=9), factitious illness (n=7), eating disorder (n=10), and previous involvement with a psychiatrist (n=7). Management of the abusing parents is complex, but recognition of their psychosocial characteristics may allow earlier diagnosis.

Imposed upper airway obstruction should be considered and excluded by physiological recordings in any infant or young child with recurrent cyanotic episodes. If physiological recordings fail to substantiate a natural cause for episodes, covert video surveillance may be essential to protect the child from further injury or death.

Suffocation by parents of their offspring is recognised as a dangerous form of child abuse.[1–4] It may present as recurrent cyanotic episodes, recurrent life threatening events, or progress to sudden and unexpected death. A parent, usually the mother, but sometimes the father,[5] may abuse one or more of her/his children for prolonged periods of time before the diagnosis is made.[6]

A diagnosis of imposed upper airway obstruction is difficult to substantiate. Covert video surveillance (CVS) has been used in this situation,[7 8] being of particular value in obtaining sufficient legal evidence to guarantee the safety of the child.[9] Our use of this technique in patients presenting with recurrent cyanotic episodes has produced information on the psychopathology of the abusing parent. This may help physicians to consider the possibility of suffocation by a parent early in the clinical course of this problem.

Table 1 Clinical details of infants subject to imposed upper airway obstruction

Case No	*Sex of infant*	*Age at onset of cyanotic episodes (months)*	*No of times admitted to hospital*	*No of episodes requiring resuscitation**	*No of siblings*	*Previous sudden infant death*
1	M	0·8	6	>20	2	No
2	F	0·8	5	7	1	No
3	F	2·5	6	5	0	No
4	F	3·8	6	8	2	Yes
5	M	10·0	19	7	2	No
6	M	1·3	5	4	1	No
7	F	4·0	3	7	0	No
8	F	33·0	6	8	1	No
9	M	1·5	4	4	0	No
10	M	0·8	4	2	4	Yes
11	F	4·0	3	>20	3	No
12	M	1·0	5	2	0	No
13	M	1·0	6	4	2	No
14	F	0·8	3	3	1	Yes

*Needing mouth to mouth resuscitation or vigorous stimulation.

Patients and methods

Between March 1986 and February 1991, 14 patients were diagnosed as having imposed upper airway obstruction. They had been referred to our department for the investigation of their recurrent cyanotic episodes at between 1·5 and 33 months (median 5·5 months) of age (table 1). The patients had been admitted to their local general and/or teaching hospitals between three and 19 (median five) occasions. Numerous investigations had been performed on these patients before referral, including barium studies, oesophageal pH monitoring, lumbar punctures, computed tomograms, and numerous venepunctures. Twelve sets of parents had been issued by their paediatrician with a breathing movement monitor (Graseby) for use at home to detect further 'apnoeic' events.

The accuracy of the details of the cyanotic episodes is dependent in part on the histories obtained from the perpetrators of the abuse. Cyanotic episodes were reported to have commenced at a median age of 6 weeks (range 0·8–33 months). Each patient was described as having suffered between two and 30 episodes, including a total of 34 requiring mouth to mouth resuscitation with/without external cardiac massage. In each patient, between one and 10 cyanotic episodes (median three, total 55) requiring vigorous stimulation, additional inspired oxygen or cardiopulmonary resuscitation, were definitely witnessed to have occurred (but not observed to begin) by nursing and/or medical staff in either the referring or our own hospital.

These patients had a total of 13 siblings and six half siblings, including three who had previously died suddenly and unexpectedly. The suspected perpetrators of the abuse included 12 mothers, one father, and one grandmother. Eleven of the infants had married parents, one of whom was separated. For the remaining three patients, one had a parent living with a common law spouse and two had single parents. The grandmother who was suspected of performing the abuse was the mother of one of these single parents and was herself living with a common law spouse.

Imposed upper airway obstruction was considered to be the likely diagnosis at the referral of eight of the 14 patients. One of these eight patients had petechial haemorrhages on the face and neck after a cyanotic episode. Their paediatricians did not consider, however, that they had sufficient evidence to confront the parent confidently and be sure of securing the long term safety of the child. The remaining six patients were referred for the management of recurrent cyanotic episodes considered to be due to a natural pathophysiology.

PROTOCOL FOR INSTITUTING CVS

When the circumstantial evidence was sufficient to suggest imposed upper airway obstruction, an informal multidisciplinary case meeting was held in order to decide whether to institute CVS.[8] This meeting involved medical, nursing, social services, and administrative staff from the Royal Brompton Hospital, local police officers (usually including the detective chief inspector), and members of the medical, nursing, and social services staff from the referring hospital. Approval for the use of CVS was given by the ethics committee of the Royal Brompton Hospital and an external working party.[9]

The evidence upon which it was considered appropriate to proceed with CVS included, firstly, that all episodes had started in the presence of the same person (as far as could be clarified) and, secondly, that there was a characteristic pattern on the physiological recordings during a cyanotic episode.

Although it was usually apparent that episodes only began in the presence of the abusing parent, it was not uncommon for members of staff to report that they had witnessed cyanotic episodes. It later transpired that the *onset* of the episode invariably occurred only when the parent was left alone or unobserved with the child. In one case, where the grandmother was inducing the episodes, the mother had reported that she had seen an episode begin. This was later considered to be her lack of appreciation as to what constituted the beginning of an episode.

Long term multichannel physiological recordings, lasting for between 12 hours and three weeks, were used to exclude or suggest imposed airway obstruction.[10] These involved recordings of arterial oxygen saturation (SaO_2) from a pulse oximeter (Nellcor N-200) modified to give beat to beat measurements, the photoplethysmographic waveforms from the pulse oximeter to verify SaO_2 measurements, breathing movements from an abdominal volumatic capsule (Graseby), electrocardiogram, heart rate, and airflow from a nasal thermistor. In some cases, two channel electroencephalogram (centrotemporal in origin) was recorded.

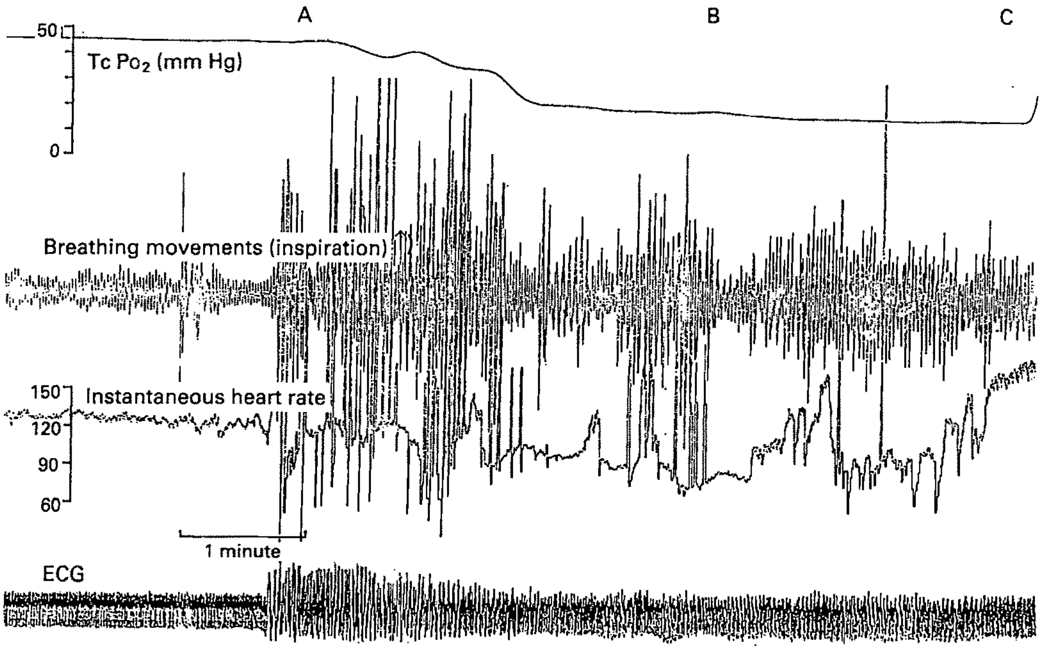
A pattern considered suggestive, but not diagnostic, of imposed upper airway obstruction has been previously reported.[7 8] Usually the recording showed regular breathing which was suddenly interrupted by the onset of large movement artefact on the breathing movement signal in combination with a pattern of obstruction—that is, continued breathing movements, absent airflow, and a gradual fall in SaO_2. In addition, there was an initial sinus tachycardia, followed by a bradycardia when severe hypoxaemia supervened.

In two of the 14 patients, cyanotic episodes failed to occur during their first admission to the Royal Brompton Hospital. As their episodes were initially considered by us to be due to natural causes, these patients were discharged with home monitoring equipment which detects sudden, potentially life threatening falls in transcutaneous oxygen tension.[11] In one of these patients (case 13), the monitor incorporated an event recorder that stored transcutaneous oxygen tension, breathing movements, and electrocardiogram in the event of an alarm. Both patients were readmitted because of further life threatening events; in the child on the event recorder, data was recorded during a major life threatening event at home requiring mouth to mouth resuscitation by the father and ambulance staff (figure).

After a decision by the planning meeting to institute CVS, this was started in our own unit in 10 cases and at the referring hospital in four cases. In our own hospital, the surveillance equipment was established by the Metropolitan Police Technical Services Department, contacted via the detective chief inspector who had attended the planning meeting. When CVS was undertaken in the referring hospital, medical staff from the Royal Brompton Hospital and police officers already experienced in this technique helped to institute and manage the surveillance.

Surveillance was undertaken by installing one or two cameras (details unavailable due to police confidentiality), obscured from normal view, in the ceiling and wall of the cubicle in which the patient was nursed. When one camera was used, this was placed within a false ceiling directly over the infant's cot at a height of about 2·8 metres above the floor level. To prevent the camera overhead being obscured by the parent leaning too far over the cot, a wall camera was also installed at a height of 1·8–2·0 metres above the floor, directly opposite and 1·5–2·0 metres from the end of the cot. To continue surveillance at night, a low level light remained on above the cot.

Both cameras were connected to a video monitor (Hitachi VM-920K) and video cassette recorder (Sony Betamax VCR SL-HF 950) in an office close to the patient's cubicle. Two women police officers (to allow for one to leave the office for essential activities), working eight hour shifts, continuously observed and recorded the patient's activities. The six police officers required in any 24 hour period were usually supplied from the police station local to where



Section of an ambulatory four channel analogue tape recording (Medilog) of transcutaneous oxygen tension ($TcPo_2$), abdominal breathing movements, instantaneous heart rate, and electrocardiogram (ECG) on a 2·5 month old infant at home (case 13). A severe cyanotic episode occurred, necessitating mouth to mouth resuscitation by the father, followed by bag and mask ventilation by ambulance personnel. This infant's episodes were subsequently proved by CVS to be due to upper airway obstruction imposed by the mother. A large amplitude signal artefact occurred at the onset of the episode (A), indicating large body movements while the infant struggles against a sudden airway obstruction. The $TcPo_2$ falls to below 20 mm Hg (2·67 kPa; duration 3·7 min), coincidental with the heart rate falling to 70 beats/minute (B). Tachycardia occurs at recovery (C), at which point the $TcPo_2$ sensor becomes detached from the skin.

the surveillance was being performed. In addition, a registered mental nurse sat in on the surveillance in seven cases, in order to deal with any distressing response manifest by the parent. The patient was maintained within view of the camera(s) by being continuously attached to the physiological recording equipment, which was established in such a way that the infant was retained at all times on the cot.

A relatively senior member of the nursing staff was selected from each nursing shift to remain within close proximity of the patient's cubicle. When police officers had observed the parent suffocating the patient for between 10 and 15 seconds, they alerted this nurse, either by direct contact or by a portable intercom, depending on the proximity of the office to the cubicle. The nurse then entered the cubicle and, as a priority, ensured that the patient's medical condition was satisfactory. This resulted in a delay of approximately 15–25 seconds from the onset of the airway obstruction before the episodes were interrupted. From past recordings of physiological data during unobserved events it had been established that hypoxaemia sufficiently severe as to cause electroencephalograph changes indicative of cerebral hypoxia occurred 50–70 seconds after the onset of obstruction.[7 8] This delay was therefore considered sufficient to allow the video evidence to be adequate for legal purposes, but without the risk of cerebral hypoxia.

PSYCHIATRIC OBSERVATIONS

At the beginning of surveillance, contact was made with a psychiatrist from the patient's locality, so that immediate assessment and follow up of the perpetrator could be achieved after diagnosis of the abuse. These 14 different psychiatrists were later contacted, their records were examined and consensus achieved on the main diagnostic categories. To verify reports given to the psychiatrists by the parents, additional information was obtained from the general practice records of the perpetrator and the social service departments local to the referring hospitals.

Results

During CVS, the nursing staff and police officers commented on how little the parent handled, played, and talked to the child when alone in the cubicle. Just before the attempt at suffocation, the parent often became still and watchful, usually for several minutes, before organising the patient's position in the cot, and, in two cases securing a blanket over the chest and arms in an attempt to restrain the child.

CVS was required for between 15 minutes and 12 days (median 24 hours) before suffocation was identified (table 2). The patient usually lay face up in the cot while the parent, having ensured that no interruption was likely to occur, occluded the airway by firmly covering the mouth and nose with one or both hands (n=9), an article of the patient's clothing (n=2), a piece of cotton fabric (n=1), or a length of domestic plastic film (n=1). In the remaining patient, fingers were inserted into the back of the mouth. In all cases, the patient struggled violently, but either the continual pressure on the infant's face or the holding of the infant's arms limited the ability of the patient to overcome the assault. No patient showed facial

Table 2 . Details of abuse, CVS, and outcome for infants and siblings

Case No	*Age at discovery of abuse (months)*	*Duration of abuse (months)*	*CVS in referring hospital or RBH**	*Duration of CVS*	*Outcome for infant*	*Outcome for siblings*
1	21	20	RBH	18 hours	Adopted	With father
2	6	5	RBH	4 hours	With parents	With parents
3	5	2·5	RBH	48 hours	Adopted	Nil
4	7·5	3·7	RBH	12 days	With parents	With parents
5	17	7	RBH	24 hours	Adopted	With parents
6	3	1·8	RBH	48 hours	Adopted	With parents
7	5·5	1·5	RBH	1·5 hours	Adopted	Nil
8	34	1	Referring hospital	36 hours	Adopted	Adopted
9	6·5	5	RBH	45 mins	Fostered	Nil
10	1·5	0·8	Referring hospital	9 days	With mother	With mother
11	10	6	Referring hospital	15 mins	Fostered	Fostered
12	7·5	6·5	Referring hospital	24 hours	Adopted	Nil
13	3	2	RBH	3 hours	With father	With father
14	4	3·2	RBH	29 hours	With parents	Deceased†

*RBH, Royal Brompton Hospital.
†See table 1.

markings which lasted more than 30–60 seconds after the attempt at suffocation.

After recording the abuse, a senior doctor (MPS or DPS) and a senior police officer reviewed the video tape to ascertain that the evidence was adequate for legal purposes. This was usually achieved within 30 minutes of the attempted suffocation, during which time CVS continued and/or a nurse stayed with the patient and parent. In six instances on five patients, it was initially considered that the recording was inconclusive, either because the view was less than adequate or the observers had interceded a little too early. In these cases, surveillance was continued for between five minutes and five days, until a conclusive attempt at suffocation was recorded.

Subsequently, the parent was interviewed by the doctor who reiterated the severity of the episodes and asked if the parent could explain their cause (this was done before the existence of video evidence was revealed). In all 14 instances the parent denied any involvement. The doctor then informed the parent that definite evidence of suffocation had been obtained.

The doctor then introduced the police officers, explaining that they had been involved in obtaining the evidence. The parent was charged with assault and escorted to the police station. When the police officers revealed the presence of video evidence, most parents admitted their participation in the observed episode. They all continued to deny or minimise, however, the seriousness of their behaviour, any intent of harm, and any part in inducing previous episodes. A few parents stated that they had performed the abuse in order to make it clear to the medical staff that their child did have a major medical problem. Alternatively, parents stated that they had merely been playing with or handling the child; one of these persisted with the idea that the child was being played with even after the court case had found her guilty.

Table 3 Characteristics of abusing parents

Case No	*Sex of abusing parent*	*Age of abusing parent (years)*	*History of abuse as a child*	*History of eating disorder*	*History of self harm*	*History of factitious illness*	*Previous involvement of psychiatrist*
1	F	24	Yes	Obesity	No	No	No
2	F	22	Yes	Anorexia	Overdoses	No	No
3	F	20	Yes	Anorexia	Overdoses	Yes	Yes
4	F	22	Yes	Anorexia	Yes	No	Yes
5	F	30	ND	Nil	Yes	No	Yes
6	F	26	Yes	Obesity	Overdoses	Yes	Yes
7	F	19	Yes	Obesity	Overdoses	Yes	Yes
8	F	24	Yes	Nil	No	No	No
9	F	18	ND	Nil	No	No	No
10	M	26	ND	Nil	Yes	Yes	Yes
11	F	20	Yes	Anorexia	Overdoses	No	No
12	F	18	Yes	Anorexia	Overdoses	Yes	Yes
13	F	25	Yes	Obesity	No	Yes	No
14	F	39	Yes	Obesity	No	No	No

ND, None disclosed.

After an appearance before a magistrate, bail was given in 12 cases. Although not a condition of the bail, the magistrates recommended that the parent undergo psychiatric assessment. Two parents were remanded in custody: one was given bail after a week (case 7), while the other (the only father) was held on a charge of attempted murder of this infant (case 10) and actual murder of a previous one. Excluding the grandmother in case 14, who is awaiting trial, 11 out of 13 parents subsequently pleaded guilty in court. All 13 were found guilty; 12 were given probational sentences and one (case 10) was given a life sentence.

All patients were subsequently transferred via the local hospital into the care of the local social services department. Case conferences were held to establish a child protection plan. There were clearly serious risks in leaving the patient in the care of the abusing parent.[3, 12] It was considered that this risk might be acceptable in the future if there was evidence of a change in the parent's attitude—as documented, for example, after psychotherapy.[13] In some cases the parents of the abusing parent requested care and control of the patient. This was rejected as it was considered likely that some responsibility for the abuse may have resulted from their poor parenting during the abuser's childhood. It was also considered that the siblings of the patient were at risk of abuse and appropriate supervision and care was provided for them through the social services authority.[3, 7]

Patient outcome is summarised in table 2. Cyanotic episodes did not recur in any patient after diagnosis of the abuse, further confirming their unnatural mechanism. At present cases 9 and 11 are fostered, pending the final decision of High Court proceedings. Six out of 19 siblings remain in the care of the abusing parent.

After disclosure of the abuse, three parents underwent inpatient psychiatric assessment (two of whom continued as outpatients) and seven received regular follow up. In four cases, only a single assessment by a psychiatrist was undertaken. Psychosocial data on the abusing parents are summarised in table 3.

PARENTAL HISTORY

A history of abuse in their childhood was obtained from 11 parents. This was confirmed by previous social service records in seven. A history of childhood sexual abuse was disclosed by seven parents and may have occurred in a further two cases. The perpetrator of this sexual abuse had been the stepfather in three cases (in one of these, older stepbrothers had also been involved), grandfather in two cases, father in one case, and uncle in one case.

Physical abuse was disclosed in seven cases: five by a male parent, four of whom were involved in the sexual abuse, and two by the mother. In one additional parent, there was a history of severe emotional abuse (possibly also with sexual abuse). For all cases, there was a history of impaired or inadequate parenting as a child: their own parents were frequently described as strict and overprotective, allowing little emotional expression. The parents of cases 4, 7, and 11 were in local authority care during their childhood, including a combination of children's homes and foster care; this was at the age of 8–16, 13–17, and 12–16 years respectively.

Nine of the perpetrators had well documented histories suggestive of a conduct disorder. These included faecal smearing (case 12), petty crime (cases 2, 4, 5, 7, 10, and 13), running away from home (case 9), teenage prostitution (case 13), and suspected arson (case 13). Nine parents had definite histories of self harm: six had taken overdoses of medication, one had swallowed bits of razor blades and carpentry nails (case 10), and one had mutilated her arms and wrists (case 4). On diagnosis of the abuse, one parent pulled out her toenails (case 5). Seven parents had a history of factitious symptoms: this most commonly involved undiagnosed 'fainting fits' during teenage years.

Ten of 14 parents had eating and/or weight problems: five had previously seen medical practitioners for anorexia and weight loss (three of whom had also been diagnosed as anorexic), and five had been grossly overweight.

Seven parents had at some time in their past consulted a psychiatrist: two for anorexia, two for depression, and three for child psychiatric problems relating to their conduct disorders.

Cases 1 and 2 have been previously described in detail.[8] For the remaining 12 abusing parents clinical features, additional to those in table 3, are described below. The details are known to be authentic, except in the case where it is stated that the parent (perpetrator) reported, alleged, or disclosed the information.

Case 3

This mother was the middle of three children. Her own mother was an anxious woman who would take to her bed for days at a time, and her father was a rigid man with high expectations. She denied any abuse as a child, although she reported emotional maltreatment. She suffered from numerous vague complaints (for example, abdominal pain), which resulted in frequent absence from school. Despite a history of teenage depression, overdoses of paracetamol, hyperventilation, fainting episodes, and anorexia nervosa she progressed well at school and obtained three 'A' levels. Contraceptive failure led to pregnancy and forced a marriage. Her child is now adopted, and she and her husband continue to live in her parents' home.

Case 4

This mother was one of three children, all by different fathers. She had a long history of conduct disorder and was in local authority care between 8 and 16 years of age. She developed severe variability in her weight and had been seen by a psychiatrist for an eating disorder. She had also mutilated her arms and wrists. At 17 years of age she married a man 30 years her senior. Her previous child had died two years before the present case, suddenly, unexpectedly, and without explanation at the age of 3·5 months. After the abuse was diagnosed, she disclosed a history of childhood sexual abuse by her stepfather. The abused child and an unaffected older brother were cared for by foster parents until the latter was returned six months later and the affected child four months after that. The mother was described as having 'matured considerably'.

Case 5

This mother was described as having strict Salvationist parents. Her father was in the armed forces. She did not report childhood abuse. Between 13 and 19 years of age, she had 'fits' which were thought to have a 'strong hysterical component'. At 15 years, she was seen by a child psychiatrist for lying and stealing, interpreted as a rejection of her parents' strict Salvationist principles.

Case 6

This mother, an only child, reported a poor relationship with her parents. At 6 years of age she had been sexually abused by an uncle. Between 12 and 16 years she was diagnosed as having 'psychogenic fainting fits'. She underwent two brief psychiatric admissions: at 17 after an overdose and at 23 when she presented 'depressed'. She had a wide variation in her body weight and was grossly overweight at the time the abuse was diagnosed. After diagnosis, she is considered to 'have progressed well' with restoration of normal body weight.

Case 7

This mother was rejected by her own mother at an early age. She was in local authority care between 13 and 17 years because of being 'out of control'. She reported sexual abuse by her stepfather, had a long history of being severely overweight, and had numerous admissions after overdoses, feigned asthma, and spurious claims of labour throughout pregnancy. She was a single mother, whose baby was made a ward of court shortly after birth because of concerns about her parenting ability. The mother was given unsupervised access one night a week to the infant when she was 4 months old, whereupon the cyanotic episodes began. After diagnosis of the abuse she was remanded in custody for one week. The registered mental nurse observing the video screen reported 'that the infant appeared a happy and active child. When her mother approached her, however, she became quieter and for long periods stared in the direction of the mother. After the abuse, the infant was very distressed initially, but subsequently quiet and unmoving'.

Case 8

This mother was the youngest of five children: her mother was reported as being strict and overprotective. She reported frequent beatings as a child, was unable to be left alone or to mix with other children. No history of sexual abuse was disclosed. At 21 years of age she married a man dependent on alcohol, but she continued to live in her mother's home. During the pregnancy, she planned to have her child adopted, but subsequently changed her mind. Before the cyanotic episodes began, the baby was admitted on several occasions with failure to thrive: no organic cause had been found.

Case 9

This mother was an only child, whose parents separated when she was a teenager after a stormy, violent marriage. Her own mother was described as a vulnerable and emotional woman and extremely demanding. No history of childhood abuse was disclosed. At 16 years of age she ran away from home, married a young, violent, man dependent on alcohol and had an unplanned pregnancy. After confrontation and a court case, both the mother and the maternal grandmother have persistently denied that the child had been harmed (they have not seen the video recording of the abuse).

Case 10

The perpetrator of the abuse in this case was the father. A child by his cohabitee's previous relationship had died suddenly two years earlier after recurrent, unexplained cyanotic episodes which had always occurred in his presence. He had a history of feigning abdominal pain and seizures as well as ingesting metal such as nails and pieces of razor blades. He had a previous psychiatric hospital admission, claiming to be depressed, but discharged himself after two days. He had also falsely claimed to have leukaemia. He had a poor work record and had used false references to obtain employment.

During the CVS and before imposing upper airway obstruction, he was observed to abuse the infant verbally and physically. This included painfully pinching and waking the baby and sticking his fingers down the child's throat. He eventually pleaded guilty and was sentenced to life imprisonment for attempted murder of this infant and for the murder of the previous infant.

Case 11

This mother was born to an English mother and a Pakistani father who separated when she was a baby. There was a series of stepfathers, one of whom along with his sons sexually and physically abused her. She was rejected by her mother from an early age and spent several years in the care of the local authority. She had a problem with school truancy, took overdoses of medication on several occasions, and was seen by her family physician for anorexia. At 17 years, she married a Muslim man, became pregnant, failed in her attempt to induce an abortion, and the resulting child became the abused child. An older sibling appeared to be unaffected. Before starting the CVS, the child was nursed in a cubicle near to the nurses' station for 12 days with no cyanotic episodes. The mother was then left alone with the child and CVS started: 15 minutes later she was seen to smother the infant.

Case 12

This mother is one of three children whose family were 'well known to the social services'. Her parents separated when she was 5 years old and she was described as having limited parenting with physical abuse by her mother. She had attended a school for behaviourally disturbed children, where she smeared the wall with faeces. She also had a history of cruelty to pets. At 16 years she alleged rape but no police prosecution followed, and at 17 years she and her sister were put on probation for abducting a baby from a local hospital. Around this time she took an overdose of medication and also attended her general practitioner for anorexia. During the pregnancy she had numerous 'collapses' which were thought to be psychogenic in origin.

Case 13

This mother had three children, the eldest of whom had previously failed to thrive. As a teenager, she had alleged rape on two occasions, but these allegations had turned out to be false. She had also alleged blackouts and a seizure, which could not be medically substantiated. She was suspected of setting fire to her own home and of making anonymous phone calls to the social services about her own children being at risk of abuse. After diagnosis she continued to deny any responsibility for the abuse. She was seen on one occasion by a psychiatrist and refused any further follow up. She has since separated from her husband, who now cares for their children.

Case 14

This case involved the maternal grandmother. She had suffered an unhappy childhood including sexual and physical abuse by her father, who drank heavily. Her own daughter was a single parent when the first grandchild was born (the patient's brother) and most of his care was given by the grandmother. This child had recurrent, life threatening cyanotic episodes from the age of 3 weeks until his sudden death during a typical cyanotic episode at the age of 11 months. All of these episodes began in the presence of his grandmother. On numerous admissions to hospital this infant had subtherapeutic levels of anticonvulsants. The grandmother offered to take over care for the subsequent child soon after she presented with similar cyanotic episodes, because the mother was frightened about caring for her new daughter, considering that she might also die during one of her cyanotic episodes. The grandmother had moved house on many occasions and it was difficult to obtain accurate records of her medical history.

The psychiatric diagnosis made in all cases was that of a personality disorder. Parents' attitudes and behaviour have appeared to improve in two cases, in one thought to be due to the psychotherapy given by the psychiatrist (case 2). Since the abuse five sets of parents have separated from their spouses.

During the five year study period, there was one further case in which CVS was performed. This case was a subsequent sibling from a family in which there had been three sudden unexplained infant deaths. After reports of two cyanotic episodes at 6 weeks and 3·5 months of age, the child underwent CVS lasting for eight days when 5 months old. No episodes occurred during surveillance, but this child was later made a ward of court after a confession by the mother that she had caused the other three deaths—a confession that was subsequently retracted.

Discussion

Imposed upper airway obstruction or suffocation is a dangerous form of child abuse with a high risk of sudden death. Meadow recently reported 27 index cases of parental suffocation and 33 siblings; in all there was an overall mortality of 45%.[3] Cyanotic/apnoeic episodes or seizures had occurred in 82% of the cases and dead siblings.[3] In addition to the risk of sudden death, such patients are at risk of hypoxic cerebral injury and may suffer significant psychological morbidity; subsequent behaviour disturbance is common.[12] The risks of similar abuse to siblings is high.[6 12]

When infants or young children present with recurrent cyanotic episodes, the physician usually assumes the parent to be truthful. Under certain circumstances, however, the physician must decide whether the story the parent gives is one of overexaggeration, entirely factitious symptoms, or real symptoms occurring as a result of abuse.[14] Physiological recordings may help to differentiate between these different situations, particularly if data can be recorded *during* the episodes.[7 8] This form of documentation may be invaluable not only as evidence to confirm abuse, but also to distinguish between a factitious history (no pathophysiology), a history of real symptoms (natural pathophysiology), and a history of real, but imposed symptoms (unnatural pathophysiology). If cyanosis or hypoxaemia has been observed by someone other than the parent who has given the history, or has been documented by physiological recordings or acid–base disturbance, and could possibly be the result of the parent suffocating the child, then the physician must consider action to ensure the child's safety.

Direct confrontation with the parents may result not only in denial by the parent (as found in all 14 of our cases before the CVS evidence was revealed), but also in loss of medical follow up for the infant and thereby an inability to secure safety for the child—that is, removal of the child from the abusing parent.[15] Leaving the child with the parent, even under close supervision by social workers, may be dangerous, particularly as continuation of abuse may occur in hospital and after discovery, indicating 'poor parental control of the impulse to harm the child'.[12] Confirmation of the diagnosis has to date usually been reliant upon circumstantial evidence, but this may be insufficient in court to ensure protection of the child.[9] The court may wish, for very good reasons and in the absence of definitive evidence, to continue child rearing within the biological family. All 14 parents in this report were extremely plausible and in many cases possessed considerable charm. Without unequivocal evidence, they could have argued their case effectively in court.

To secure unequivocal evidence and thus obtain legal separation of the child from his/her abuser, video tape evidence during a typical cyanotic episode was collected.[7 8] The performance of video surveillance without parental knowledge is clearly an infringement of trust between the paediatrician and the parents.[9] Before commencing CVS, therefore, there should be a *strong* suspicion of abuse, although the information upon which this is based will usually be insufficient to guarantee that a court will separate the child from its parents. Above all, CVS is performed because the prime concern of the paediatrician is for the rights of the child. In retrospect, a positive result from CVS can then, in our opinion, be considered justified. To date, no child has undergone CVS and found to have a natural (non-abuse) cause for their cyanotic episodes.

Meadow has suggested that CVS may have a low sensitivity for detecting parental suffocation as the infant may not suffer a cyanotic episode while in hospital and under surveillance.[3] In all but one of the 15 patients undergoing CVS after referral to our unit with recurrent cyanotic episodes considered to be due to suffocation, parents have attempted to induce episodes while in hospital and within close proximity of staff. It also became clear that parents were more likely to impose airway obstruction when, due to close nursing observation, they had been unable to demonstrate their child's 'symptoms' for a period of time. The median duration of surveillance required before diagnosis was 24 hours—fortunately short in view of the staffing and equipment required to perform CVS.

Despite unequivocal video evidence of suffocation, some magistrates and judges expressed incredulity that a parent could have performed such behaviour on their child. Once again this fact highlights the need to obtain, whenever this can be achieved, unequivocal data in all cases of child abuse, particularly when this involves recurrent suffocation.

The underlying reasons why parents abuse their children in this way remain unclear. A behaviour pattern in which symptoms or signs are fabricated in children has been given a variety of labels, including most commonly, Munchausen syndrome by proxy. However, unlike adults with Munchausen's syndrome, these parents have not invented a variety of progressively more bizarre symptoms and did not appear to seek out intentionally a number of different specialists. In our cases, the parent had usually identified only one paediatrician to look after the child's problem before referral.

Psychiatric evaluation of offending parents has not been well documented. In the case of childhood poisoning, Rogers *et al* hypothesised that the parents may have been creating a situation which enables them to escape from there own physical or psychological illnesses, marital or social problems.[16] This does not appear to explain, however, the form of abuse seen in these present patients. Thus none of the parents appeared to have encountered a new stress in their life situation. In addition, these parents did not appear to smother the child in anger or in an attempt to silence them: their actions appeared well thought out and were performed calmly and carefully.

Meadow has previously reported that 18/47 of abusing parents had themselves reported factitious illness or symptoms,[17] and Alexander *et al* reported this in four of five mothers.[6] Nine of our 14 cases had a history of previous factitious illness or self harm. This behaviour may stem from a low self esteem, resulting from early childhood experience such as poor parenting or frank abuse, as so explicitly reported in 11 out of 14 of these cases. Meadow reported a history of sexual or physical abuse in childhood of at least 25% of the parents performing these acts.[3] He also reported possible emotional abuse in 70% of cases.

Poor parenting may make it difficult for a child to develop normal emotional expression and, in adulthood, this may result in difficulties in differentiating her/his own emotions from those of the infant. If the mother tends to harm herself, then the child may also be at risk of harm. Clearly the drive to be harmed or cause harm must be strong; it may be a form of self inflicted punishment for having been such a 'problem' for their own parents or not conforming to their parents' expectations. The attachment to, and conflicting emotions for, the abused infant may be less likely to play as important a part in the two cases in which the father and grandmother were the perpetrators. These cases both involved previous sudden infant deaths and appear to be even more complex.

In an assessment of mothers who had fatally abused their children, Korbin found a history of childhood maltreatment, predominantly physical, to be the most consistently reported characteristic in the parents.[18] Tuteur and Glotzer also found severe childhood emotional deprivation in a study of mothers committing infanticide.[19] It remains unclear how commonly a history of childhood maltreatment results in this intergenerational cycle of abuse. There may be many parents who, having been abused in their own childhood, never abuse their own children. Prospective work on child rearing practices may help to determine how often abuse in early childhood results in this form of abuse.

Eating disorders have not previously been reported in parents who suffocate their children. Lacey and Evans have reported that bulimia is associated with multi-impulse behaviour.[20] Many of the abusing parents demonstrated this behaviour in, for example, overdosing, self mutilation, stealing, fire setting, and petty crime. The significance of eating disorders in parents who suffocate their babies is unknown, but it might be considered as a form of self harm. Similarly, the proportion of impulsive women who harm their babies in this way is unknown.

All our abusing parents received a primary diagnosis of 'personality disorder'. This is a vague and unsatisfactory label as it adds little to our understanding of the psychopathology of these parents. Furthermore treatable mental disorders (for example, depression and anorexia) were often omitted from the final diagnosis, when they appeared to be frequently described in the psychiatric histories. Possible reasons for this discrepancy include the difficulty in differentiating genuine from factitious symptoms in some cases. A severe personality disturbance may predominate over the presentation or detection of other mental disorders. These factors may contribute to the frequency, yet variable and inconsistent nature of psychiatric input in the cases of our perpetrators.

Before a diagnosis of the abuse, seven out of 13 parents had been attended by psychiatrists, a similar finding to the four out of five cases reported by Alexander *et al*.[6] No common approach was identified. Treatment was considered by many psychiatrists as unlikely to modify outcome, particularly when the parent showed little insight into the seriousness of her behaviour or lack of commitment to treatment.[13] There is inevitably a reliance on abusing parents telling and appreciating the truth of their childhood experiences, not only in any psychotherapeutic situation but also in any assessment. Even if the psychiatrists find it hard to treat the underlying personality disturbance, their involvement may help to understand further the reasons why parents suffocate their infant and to guide the courts in their decision making.

In conclusion, the parents of all infants and young children with recurrent cyanotic episodes should undergo careful and incisive history taking to establish whether the episodes have been seen to begin other than in the presence of one carer. If at all possible, it is important to document the pathophysiology of episodes by physiological recordings during a typical episode. When imposed upper airway obstruction is suspected, action must be taken to ensure the safety of the child. This can be done by CVS, but in our experience, confrontation without unequivocal evidence will fail. The involvement of psychiatrists in unravelling the psychopathology could be of great value in further understanding why this form of abuse occurs and assisting the courts in deciding if and when to return an infant to its abusing parent. Finally, long term studies of child rearing practices are needed to help establish the role of poor parenting in the development of this dangerous behaviour.

We thank all staff who were involved with these cases, particularly the nursing staff who cared for the patients during covert video surveillance and the police officers and detectives at Chelsea Police Station. We are also grateful to Drs Bush, Reddington, and Shinebourne, and Professor Warner who helped in the clinical management of these patients. Dr Samuels is funded by 'Little Ones', Dr Poets by Deutsche Forschungsgemeinschaft, FRG, and Dr Southall by the National Heart and Lung Institute and The Foundation for the Study of Infant Deaths, UK.

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Combined effect of infection and heavy wrapping on the risk of sudden unexpected infant death

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Abstract

Three methods were used to investigate the role of infection in sudden unexpected infant death (SUD): (i) microbiological comparison of SUD victims and matched, live, community controls; (ii) postmortem classification of the contribution of infection to death; and (iii) case-control analysis of the relative risk associated with both infection and heavy wrapping.

Limited sampling from the upper respiratory tract and gut in SUD victims and controls showed no significant excess of viral infection in the SUD victims (odds ratio=1·98, 95% confidence interval (CI) 0·9 to 4·5). At postmortem examination, infection explained death in 3/95 babies and may have contributed to death in 37/95.

Over 70 days of age, the combined presence of viral infection and wrapping in excess of 10 togs produced an odds ratio of SUD of 51·5 (95% CI 5·64 to 471·48) compared with wrapping of less than 6 togs.

Viral infection was not a major risk factor as long as babies were lightly wrapped. In heavily wrapped babies the presence of a viral infection greatly increased the risk of SUD.

Infection is a common finding in babies dying suddenly and unexpectedly (SUD).[1–8] In a small proportion, overwhelming infection is clearly the cause of death, but in the majority it is uncertain whether infection contributes to death or not.[8]

Previous studies have failed to determine whether infection occurs more commonly in SUD victims than in similar infants living in the same community at the same time.[1 2 5–7] Furthermore, pathologists vary considerably in their interpretation of postmortem findings.[9 10] Lack of control babies for postmortem examination of a similar age who die from accidents has made it difficult to establish a consistent classification of those findings which explain death, contribute to death, or are non-contributory.

Although minor respiratory tract infections are the most common finding in SUD victims, there has been no association between SUD and any one particular organism.[1–8] Consequently, if infection is associated with SUD, the mechanism may be related to factors common to infection in general, such as an increase in metabolic rate and body temperature or to effects on airway patency.[11] It is possible that infection interacts with other environmental or physiological factors known to be associated with SUD, such as heavy wrapping or prone sleeping, to precipitate SUD in some babies.[12–15]

In order to assess the role of infection in SUD we have investigated the incidence of infection in SUD victims and matched controls from the same community. Secondly, we have established criteria for a classification of postmortem findings to reflect contribution of infection to death. Lastly, we have investigated the combined presence of infection and heavy wrapping on the risk of SUD.

Methods

Important features of the study design were that: all SUD victims within a defined geographical area were investigated, specimens were collected and parents were interviewed as soon as possible after discovery of death, and live control babies were matched for age, neighbourhood, and time of year.[12]

INDEX BABIES

From May 1987 until the end of April 1989, all babies between the age of 1 week and 2 years who died suddenly and unexpectedly within Avon and north Somerset were eligible for inclusion in the study.

Collection of specimens

An initial set of specimens was taken within a median time of 3·5 hours from the discovery of death (range 0·25–46 hours). Specimens included: nasopharyngeal aspirate, tracheal aspirate, four throat swabs taken simultaneously (last 58 cases only), blood taken from the sagittal sinus (all cases) and from the heart (last 70 cases only), and cerebrospinal fluid obtained by cisterna magna puncture. Urine was obtained if possible by suprapubic aspirate and a stool specimen was collected when available. Specimens were immediately transported to the laboratory and processed.

Further tissue samples and swabs of all major organs were taken at full postmortem examination, which was performed within a median time of 25 hours (range 2·8–73 hours) after discovery of death. The postmortem protocol was similar to that described by Wigglesworth *et al.*[16]

Interviews

As part of the bereavement counselling, parents were seen by one of the investigators usually within hours of discovery of death. A detailed medical history was taken including recent signs

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of illness noted by the parents. Major signs were classified as those indicative of serious illness or needing a medical opinion such as drowsiness, persistent cough, or missing more than one feed.[17] Hospital records were scrutinised for any additional clinical and demographic information. For the latter 18 months of the two year study, detailed questions were asked about the quantity and type of clothing and bedding covering the baby and the position in which the baby was lying when found dead and when put to bed. Tog values for clothing and bedding were calculated as previously described.[12] Information on daily maximum and minimum temperatures in Avon for the period of the study was supplied by the Meterological Office.

CONTROL BABIES

The next two babies born within two weeks on the same health visitor list as the index case were selected as controls. Control families were visited within a median time of 70 hours from the discovery of death (range 8–324 hours).

Four throat swabs and a stool specimen were collected and processed in the same way as for the index cases. Parents were asked to save a stool specimen for collection. In 23/190 cases, no stool specimen was received.

Control parents had similar detailed interviews to the index parents. Questions were asked about clothing, bedding, and the sleeping position during the night before interview.

LABORATORY TESTS

Viral isolation was carried out using standard cell culture and identification techniques on the following cell lines: Hep 2, baboon kidney, MRC5, and C16. Nasopharyngeal aspirates were examined using immunofluorescent microscopy with monoclonal antibodies to respiratory syncytial virus, adenovirus, influenza virus types A and B, cytomegalovirus, parainfluenzae virus types 1–3, herpes simplex virus, measles virus, and *Chlamydia trachomatis*. Throat swabs were similarly examined using monoclonal antibodies to *C trachomatis*. Faecal extracts were subjected to tissue culture and inoculated into suckling mice to culture coxsackie A virus. Faeces or large intestinal contents were examined for viruses using standard electron microscopy techniques.

Routine bacteriology was carried out on all swabs and gastrointestinal specimens. Selective media were used to culture *Staphylococcus aureus*, *Streptococcus* sp, *Bordetella pertussis*, *Campylobacter* sp,[18] *Clostridium botulinum*,[19] *Clostridium difficile*, *C trachomatis*,[20] *Ureaplasma urealyticum*, and *Mycoplasma hominis*.[21] Botulinum toxin was detected by inoculation of faeces supernatant or extract into suckling mice. Cytotoxin testing was performed using vero cell monolayers together with DNA probes for verocytotoxin genes VT1 and VT2.[22] Where appropriate, organisms were typed using commercial kits followed by reference laboratory analysis.

CLASSIFICATION OF FINDINGS AT POSTMORTEM EXAMINATION

All postmortem examinations were carried out by one of two pathologists (PJB, EH). Histological findings at six sites in the respiratory tract were reviewed and graded in all cases by PJB without knowledge of any details of the case: grade 0 normal, grade 1 mild inflammation, grade 2 moderate inflammation, and grade 3 severe inflammation.

Histological and microbiological findings for all 95 SUD victims were correlated and criteria developed for three broad categories of SUD: I: no significant findings, II: findings that may have contributed to death, and III: death fully explained by findings. These categories were further subdivided (see table 1).

All pathological, microbiological, and metabolic results were reviewed for each baby at a multidisciplinary meeting which included two pathologists, three microbiologists, and three paediatricians. Microbiological, histological, and metabolic findings were classified separately and the highest grade allocated as the overall category for each baby as shown in table 1.

STATISTICAL ANALYSIS

The Mantel and Haenszel triplet test was used

Table 1 Example of categorisation in a 61 day old SUD victim: adenovirus type 5 isolated from the large intestine but with no evidence of gastroenteritis (IB), C trachomatis identified in the nasopharynx and trachea (IIA), grade 1 inflammation on lung histology (IB), no abnormal metabolic findings (IA). Overall category allocated was IIA based on microbiological findings

Category definitions	*Histopathological criteria*	*Microbiological criteria*	*Metabolic criteria*
IA: No abnormal findings	No abnormal findings	No abnormal findings	No abnormal findings
IB: Non-contributory findings	Grade 1–3 inflammation of URT, grade 1 inflammation of LRT, purulent exudate—middle ear, minor congenital anomalies	Bacterial pathogens in LRT, non-pathogenic bacteria in blood (for example, coagulase negative staphylococci), virus excretion (for example, from faeces or urine), polio virus—any site except CSF	For example, raised octanoic acid in CSF
IIA: Associated findings, which may have contributed to death	Grade 2–3 inflammation of LRT, significant inflammation at other sites—for example, urinary tract	Bacterial pathogens isolated from blood or in heavy growth from liver and spleen or kidney, polio virus in CSF, *C trachomatis* in respiratory tract	Vitreous humour sodium <126 or >150 mmol/l, urea >8·0 mmol/l, isolated metabolic defect, (for example, glycogen storage disease type Ic)
IIB: Extensive/severe associated findings but not a complete explanation for death	Extensive grade 3 inflammation of LRT	Bacterial pathogens in blood, liver, and spleen	Metabolic defect with evidence of substrate accumulation
III: Death fully explained by findings	Severe disease—for example, purulent meningitis, pyelonephrosis, major heart defect	Bacterial pathogens in CSF	Raised serum ammonia >150 mmol/l, major metabolic defect

LRT=lower respiratory tract, URT=upper respiratory tract, CSF=cerebrospinal fluid.

to compare qualitative variables in index cases with two matched controls.[23] A modified form of this test was used where a variable number of controls were analysed.[24] Continuous variables were analysed using the paired *t* test or the Wilcoxon rank test by comparing index cases with the mean of the two matched controls. Interaction between variables was assessed using a matched multiple logistic regression programme which retained index case matching with the control pairs.[25]

Results

A total of 109 babies died suddenly and unexpectedly during the two year study period of which 95 were investigated. Fourteen were excluded mainly because of late notification to the investigators. Microbiological, pathological, clinical, and social information was collected for these 14 excluded babies and did not differ from the study group.

Of the 95 SUD victims investigated, an explanation for death was found in 7/95 (8%): intracranial haemorrhage, Reye's syndrome, heart failure secondary to an atrioventricular canal defect, gastric perforation, *S aureus* septicaemia, *Haemophilus influenzae* meningitis, and severe rotavirus gastroenteritis. The remaining 88/95 cases were classified as sudden infant death syndrome (SIDS).[26] One of these 88 SIDS victims was resuscitated and ventilated for 24 hours before brainstem death was confirmed. Of the 95 index babies, information on sleeping position and clothing and bedding was available in 72 SUD victims and 144 matched controls. Five of 72 of these deaths were explained. This subgroup of 72 SUD victims did not differ significantly from the overall study population of 95 index babies.

The median age for the 95 index babies was 94 days (range 7–551) and for the 190 controls 96·5 days (range 18–552); difference 2·5 days, 95% confidence interval (CI) 1·5 to 3·75 days. The age distribution appeared to be bimodal with peaks in incidence at 40–60 and 80–130 days and a trough at 70 days (see fig 1). In subsequent analysis the effect of age is assessed by comparison of babies older and younger than 70 days of age. Ninety of 95 (95%) index babies were less than 210 days (30 weeks) when they died.

Index babies were lighter at birth with a mean birth weight of 3230 g (range 1310–4640) compared to the control babies with 3400 g (range 1790–4840); mean difference 170 g (95% CI: 0·016 to 0·324, p=0·03). The mean gestation in the index group was 38·9 weeks (range 32–42) and in the control group 39·8 weeks (range 34–43); mean difference 0·86 weeks (95% CI: 0·36 to 1·36, p<0·001).

The male to female ratio was 1·6:1 and 1:1 in the index and control groups respectively. Index babies were significantly more likely to have one or more siblings (72/95) compared to controls (111/190); χ^2=11·2, p<0·001. Too few babies had viral infections to determine whether infection occurred significantly more commonly among babies with siblings. Twenty three percent of the babies in both groups had received their polio immunisation within the previous 60 days.

Socioeconomic classification (Registrar General's classification group I–V) was similar in both index and control groups, but there was an excess of unemployed parents in the index group: odds ratio 3·3, 95% CI: 1·6 to 7·0 (p<0·01).

Sixty out of 95 of the SUD victims (63%) died during the six month period from October to March, the peak incidence being in March. There was no relationship between age at death and season; 24/35 (69%) of SUD victims less than 70 days died during the six winter months, compared with 36/60 of those over 70 days old.

MICROBIOLOGY RESULTS BASED ON COMPARISON OF SUD VICTIMS AND CONTROLS

Comparison of microbiological results was based on similar specimens taken from the upper respiratory and gastrointestinal tracts. In addition to throat swabs and stool specimens, nasopharyngeal aspirates and specimens of intestinal mucosa were taken from index babies.

Viruses

Results of viruses detected are shown in table 2. Excluding those babies from whom no stool specimens were obtained, the odds ratio for sudden death associated with non-polio virus detection was 1·96 (95% CI: 0·9 to 4·5, p>0·05). Types of viruses identified in both groups were predominantly adenoviruses and enteroviruses. In both the index and control groups, 85% (13/15) of the virus positive babies were over 70 days old. Of the virus infected SUD victims, 7/15 were girls as were 10/15 of the virus infected controls (p>0·05).

Bacteria

The prevalence of potential bacterial pathogens in the upper respiratory tract in the SUD victims and control babies is shown in table 3. There was no association between isolation of

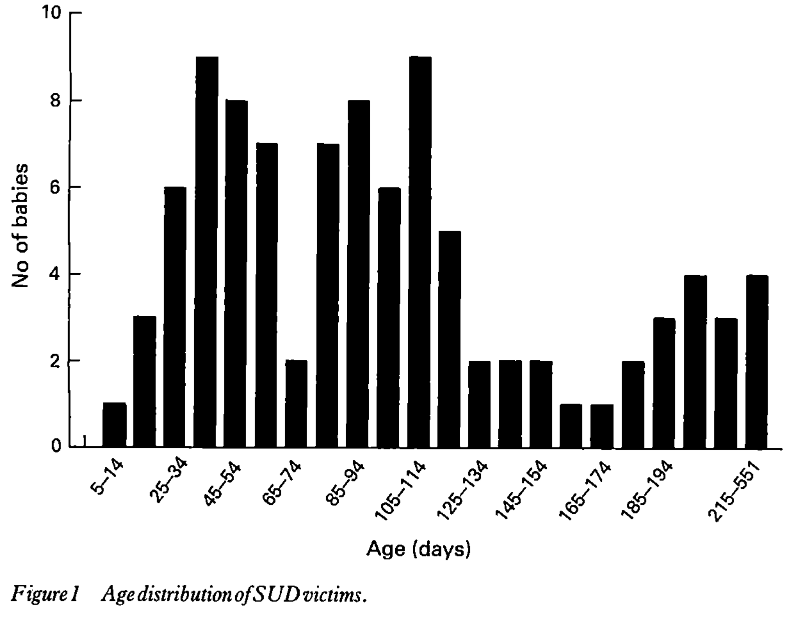

Figure 1 *Age distribution of SUD victims.*

these organisms and sampling time: median time from discovery of death for pathogen positive babies was 3·87 hours (range 1·5–45·7) and for pathogen negative babies 3·2 (range 0·25–30) (difference 0·67, 95% CI: −0·28 to 1·55; $p>0{\cdot}05$).

Faeces from 1/90 index and 1/164 control babies were positive for cytotoxin which was not neutralised by antisera to *C difficile* : one control baby was culture positive for *Escherichia coli* 074.H28 and the verocytotoxin gene 2 (VT2) probe. One index baby was positive for cytotoxin to vero and Y1 cells but negative to VT1 and VT2 probes and neutralising antibodies.

Table 2 Micro-organisms detected in SUD victims and controls (number of samples included in each analysis shown in square brackets)

Type of organism or toxin and specimen site	*No (%) of babies affected*		*p Value*
	SUD victims	*Controls*	
Non-polio viruses:			
Upper respiratory tract	8 (8) [n=95]	10 (5) [n=190]	>0·05
Gut*	10 (11) [n=95]	10 (6) [n=167]	>0·05
Total No virus positive	15 (16) [n=95]	15 (8) [n=190]	>0·05
Polio viruses:			
Upper respiratory tract	5 (5) [n=95]	10 (5) [n=190]	>0·05
Gut*	17 (18) [n=95]	25 (15) [n=167]	>0·05
Total No virus positive	17 (18) [n=95]	30 (16) [n=190]	>0·05
C trachomatis in upper respiratory tract†	4 (4) [n=95]	0 [n=190]	>0·05
U urealyticum or M hominis in upper respiratory tract	5 (8·5) [n=58]	6 (5) [n=117]	>0·05
C botulinum in gut*	0 [n=95]	0 [n=167]	>0·05
C botulinum toxin in gut*	0 [n=36]	0 [n=30]	>0·05
C difficile toxin in gut*	5 (6) [n=85]	8 (5·5) [n=142]	>0·05

*Denominator varies according to availability of sufficient specimen for testing.
†Two cases were culture and immunofluorescence positive; two cases were immunofluorescence positive only.

Table 3 Potential bacterial pathogens isolated from the upper respiratory tract in SUD victims and controls

Organism isolated	*No (%) of babies affected*		*Odds ratio*	*95% CI*	*p Value*
	SUD victims (n=95)	*Controls (n=190)*			
S aureus	24 (25)	12 (6)	5·0	2·4 to 10·2	<0·001
Coliforms	15 (16)	2 (1)	29	7·5 to 111	<0·001
S pneumoniae	10 (11)	2 (1)	10	2·9 to 34	<0·01
H influenzae	9 (9)	11 (6)	1·6	0·7 to 3·8	>0·05
Streptococcus*					
Group A	2 (2)	2 (1)	>0·05		
Group B	6 (2)	2 (1)	11	1·9 to 63	<0·01
Total No of babies affected	51 (54)	31 (16)	7·6	4·1 to 14	<0·001

*β Haemolytic streptococcus Lancefield group A or B. Note: for the first 37 index cases, results are from culture of nasopharyngeal aspirate, therafter, results refer to throat swabs only.

We found no relationship between viruses and bacterial pathogens identified at the same site. Viruses were detected as frequently in the upper respiratory tract of babies who were positive for bacterial pathogens (16%, 8/51) as in babies who had no potential bacterial pathogens isolated (16%, 7/44).

MICROBIOLOGICAL FINDINGS AT POSTMORTEM EXAMINATION: INDEX BABIES ONLY

Based on virological analysis of all organs, non-polio viruses were indentified in 19/95 (20%) babies and one further baby had poliovirus type 2 isolated from the cerebrospinal fluid. Non-polio viruses identified in order of frequency were adenovirus (n=8), enterovirus (n=3), rotavirus (n=2), parainfluenzae virus type 3 (n=2), cytomegalovirus (n=2), measles (n=1), and respiratory syncytial virus (n=1). One further baby had congenital cytomegalovirus infection, demonstrated by positive urine culture at 3 weeks of age but was culture negative at postmortem examination at 5 months old. The type and distribution of bacterial pathogens is shown in table 4. Nine babies had bacteraemia, in two cases both *H influenzae* and *Streptococcus pneumoniae* were isolated.

CLASSIFICATION OF FINDINGS AT POSTMORTEM EXAMINATION

Results for all 95 SUD victims are given in table 5. Thirty nine of 95 babies were allocated category IIA or IIB, 37/39 due to evidence of recent infection. Of these 37 babies, 11 were graded IIA or IIB on account of both microbiological and histopathological findings. Of the remaining 26 babies allocated category IIA and IIB babies, nine babies, three of whom were graded for histopathology and six for microbiology, had no corroborative microbiology or histopathology findings respectively. Nine out of 35 of the SUD victims (26%) less than 70 days old and 28/60 (47%) of those over 70 days were allocated category IIA or IIB for evidence of infection ($\chi^2=4{\cdot}08$, $p<0{\cdot}05$).

THERMAL INSULATION IN INDEX AND CONTROL BABIES

Of the 72 SUD victims and 144 controls, data

Table 4 Frequency and site of isolation of bacterial pathogens at postmortem examination

Organism isolated	*Upper respiratory tract (n=95)*	*Tracheal aspirate/swab or left/right main bronchus (n=94)*	*Lung (n=94)*	*Middle ear (n=81)*	*Liver (n=94)*	*Spleen (n=94)*	*Kidney (n=94)*	*Cerebrospinal fluid (n=95)*	*Blood (n=95)*
S aureus	24	33	7	2	1	1	2	—	3†
Coliforms	15	37	14	4	3	3	1	—	1
S pneumoniae	10	12	2	3	—	—	—	—	2
H influenzae	9	14	5	7*	—	—	—	1	3†
Streptococcus*									
Group A	2	2	1	—	—	—	—	—	—
Group B	6	8	4	1	—	—	—	—	—
Streptococcus equisimilis	1	1	—	—	—	—	—	—	1
Total No (%) of cases affected	51 (54)	72 (77)	28 (30)	16 (20)	4 (4)	4 (4)	3 (3)	1 (1)	8 (8·5)

*β Haemolytic streptococcus Lancefield group A or B.
†One explained death.

Table 5 Classification of findings at postmortem examination for 95 SUD victims

Category	*Classification*			*Total No (%) of cases*	
	Microbiology	*Histopathology*	*Metabolic*		
IA				6	49 (51·5)
IB	36	17	3	43	
IIA	19	20	4	34	39 (41·0)
IIB	1	4	0	5	
III	2	7	1	7 (7·5)	

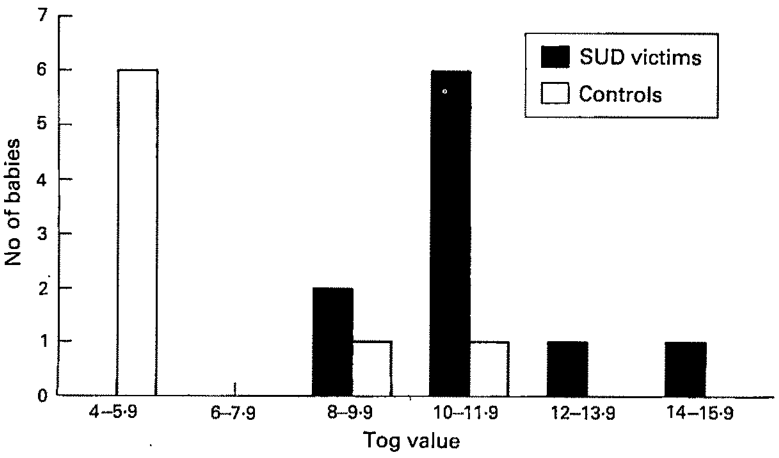

Figure 2 Tog values in virus infected SUD victims and control babies.

were incomplete on clothing and bedding in four babies and on sleeping position in five index babies. The median age of the 72 SUD victims was 90 days (range 7–210 days) and of the controls 89 days (range 18–208 days). Forty four of the 72 SUD victims were aged over 70 days when they died.

For babies in whom thermal insulation data was complete, there was no significant difference between the virus infected SUD victims (10/68) and the virus infected controls (8/136) in terms of age, birth weight, or minimum environmental temperature during the 24 hours preceding death or interview. Only one baby in each group was less than 70 days old.

Tog values

Thirty out of 68 of the SUD victims (44%) and 37/136 (26%) of their matched controls had calculated tog values greater than 10 togs (χ^2=5·9, p<0·02). Mean tog values were 9·15 and 8·0 for the index and control babies respectively, mean difference 1·1 togs (95% CI: 0·15 to 2·2, p=0·025).[12] Tog values for the babies with virus infections are shown in fig 2.

The median tog values for all virus infected babies were 11·0 (range 9·1–14·7) for index babies (n=10) and 5·6 (range 5·5–10·7) for controls (n=8); difference 4·9 togs (range 3·3–5·6, p=0·0016). There was no significant difference between the median tog values for all virus negative index babies, median tog 8·8 (range 0·8–18·4; n=58) and control babies, median tog 8·0 (range 1·9–16·5; n=128). Among babies over 70 days old, the difference in tog values between infected index (n=9) and control babies (n=7) was 4·8 togs (range 2·8–5·5, p=0·004) and for non-infected index (n=32) and control babies (n=75) 1·8 togs (range 0·5–3·3, p=0·014).

A similar relationship was found between isolation of potential bacterial pathogens and tog values. Twenty index and nine control babies over 70 days old had bacterial pathogens isolated in significant quantities from the upper respiratory tract; none of these babies had viruses identified in the upper respiratory tract. The median tog values for the bacterial pathogen positive babies were: SUD victims 11·1 togs, controls 5·6, difference 5·5 togs (95% CI: 2·0 to 7·9, p<0·01). For the babies with no bacterial pathogens isolated, the median tog values were: SUD victims 10·3 togs, controls 8·0 togs, difference=2·3 togs (95% CI: 0·1 to 2·8, p<0·05).

Analysis using a matched multiple logistic regression analysis for babies over 70 days old showed that there was a trend for virus infection to be associated with an increased risk of SUD: odds ratio=2·8 (95% CI: 0·98 to 7·9; p>0·05). When account was taken of the tog distribution, both virus infection (odds ratio 3·7, 95% CI: 1·03 to 13·3) and clothing and bedding in excess of 10 togs compared with less than 6 togs (odds ratio 13·7, 95% CI: 3·2 to 60·6) were significant, independent risk factors with no statistical interaction between them (χ^2=1·98); the relative risk for 6–10 togs was 3·9 (95% CI: 0·99 to 15·2; p>0·05). The relative risk associated with the combined presence of more than 10 togs of clothing and bedding and a viral infection compared with less than 6 togs and no viral infection was 51·55 (95% CI: 5·6 to 471).

SIGNS OF ILLNESS

In both the index and control groups over 70 days old, there was no significant difference in tog values between babies with major signs of illness during the previous 24 hours (10/41 index and 6/82 controls) and those without (difference in togs for SUD victims=0·6 and for controls=0·05; p>0·05).

Major signs of illness during the previous week were more common among virus positive (10/15) than virus negative (24/80) SUD victims (χ^2=7·3, p<0·01) but no such association could be demonstrated for the control babies.

We were unable to demonstrate the effect of the combination of prone position and viral infection as the number of infected babies was small and such a high proportion of the SUD victims (63/68) slept prone.

Discussion

There were two distinct age groups within the SUD population, infection being much more common in index and control babies over 70 days of age. In this older age group, the combination of viral infection and clothing and bedding in excess of 10 togs was associated with a significantly increased risk of death.

Based on limited sampling from the upper respiratory and gastrointestinal tracts we did not show any significant excess of virus infection in the index group (16%) compared with live control babies matched for age, time, and neighbourhood (8%). The trend for viruses to be identified more commonly in the index group may have reached significance given a larger population. However, one important source of error was the fact that nasopharyngeal aspirates and intestinal mucosa specimens were analysed only in the index group. This is likely to have favoured more frequent identification of viruses in the index babies. Although virus infection did reach significance when the distribution of tog values was taken into account using a multiple logistic regression model, these borderline results indicate that viral infection alone can not be considered to be a major risk factor for SUD.

Bacterial pathogens were isolated more often from the upper respiratory tract of babies who died but there was no association between viral presence and isolation of bacterial pathogens at the same site. We are uncertain as to the significance of bacterial isolates at postmortem examination. Correlation with histological change is poor and it is possible that changes in bacterial flora occur as a result of, rather than before terminal asphyxia and death. It is of note that we were unable to confirm the association found by Bettelheim *et al* between toxigenic *E coli* and SUD.[22]

According to our postmortem classification of findings in the index babies, infection provided an explanation for death (grade III) in 3/95 babies and may have contributed to death (grade II) in a further 37/95. This classification is subjective and although postmortem control samples from babies dying suddenly from trauma would enable a more objective analysis of postmortem findings, such deaths are very rare and none occurred during our study. Nevertheless, our criteria could provide a basis for a more consistent classification of postmortem findings in SUD.[9 10 27] An important advantage of our system is that, alongside the microbiological, histological, and metabolic classifications, other classifications can be added such as psychosocial factors, clinical factors or thermal stress, without distorting the overall categorisation of non-contributory (I), contributory (II), and causal disease (III).

On virological investigation of all organs, non-polio viruses were identified in 19/95 (20%) of SUD victims, a similar proportion to that found in previous studies.[1–5] It is of note that although the study period included two winters when respiratory syncytial virus infection was commonly identified in children admitted to hospital, we detected this virus in only one baby who died.

A striking finding was that the virus infected control babies had less clothing and bedding than the index babies and the non-infected control babies. This could not be explained by differing parental responses to illness as we found no correlation between reported major signs of illness and tog values of clothing and bedding in either the index or control groups. Another possible explanation is that light wrapping increased the risk of acquiring a viral infection while heavy wrapping increased the risk of death in the presence of infection.

Infection increases metabolic rate and can increase body temperature. The ability to lose heat in the presence of infection may therefore become critical in heavily wrapped babies. As 40% of total oxygen consumption in young infants is in the brain, the head is both a major site of heat production and the main effector organ for heat loss.[28–30] Thus interference with heat loss from the head (for example by covers rising over it) could lead to temperature change in the brain without necessarily causing a corresponding rise in core body temperature. The consequences of such a rise in brain temperature are not known, but heat stress can lead to prolonged apnoea in both preterm[31] and term infants.[32] Of our SUD victims, 23 wore a hat or were found with their head covered. Although no control babies wore hats, we have no data on how many had their heads covered by bedding at some time during the night.

Sudden unexpected infant death is undoubtedly caused by a variety of factors. In this and in a previous report[12] we have shown that prone sleeping, heavy wrapping, the combination of prone sleeping and heavy wrapping, and the combination of viral infection and heavy wrapping are strongly associated with SUD. All three factors can cause thermal stress but their association with SUD is age related.[12] The fact that infection and heavy wrapping are associated with death only in babies over 70 days old may indicate that these babies are physiologically less vulnerable and require more risk factors to precipitate death. Alternatively, older babies with their thicker subcutaneous layer of fat and higher ratio of metabolic rate to surface area[33 34] may be more susceptible to thermal stress than younger babies for whom other mechanisms may be important.

Our case-control analysis was based on a small minority of babies with viral infection. Yet our postmortem classification showed that 37/95 (38%) SUD victims had evidence of recent infection which may have contributed to death. We speculate that the combination of infection and other environmental factors that cause thermal stress may contribute to death in over a third of SUD victims.

In babies over 70 days of age, the presence of a viral infection further increases the risk of death associated with heavy wrapping. The presence of a virus infection in the absence of heavy wrapping is not a major risk factor for sudden unexpected death.

We recommend that parents should pay particular attention to thermal care and avoid heavy wrapping, particularly if their baby has evidence of an infection. Avoidance of heat stress may be easier for babies nursed on their back or side.[12] Parents should still be made aware of the need to avoid cold stress particularly as our results raise the possibility that lightly wrapped babies may be more likely to contract viral infections.

Further investigation is needed to ascertain appropriate clothing and bedding at different environmental temperatures and to define the effects of infections on metabolic rate and heat production in infancy.

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A clinical study of Noonan syndrome

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Abstract

Clinical details are presented on 151 individuals with Noonan syndrome (83 males and 68 females, mean age 12·6 years). Polyhydramnios complicated 33% of affected pregnancies. The commonest cardiac lesions were pulmonary stenosis (62%), and hypertrophic cardiomyopathy (20%), with a normal echocardiogram present in only 12·5% of all cases. Significant feeding difficulties during infancy were present in 76% of the group. Although the children were short (50% with a height <3rd centile), and underweight (43% with a weight <3rd centile), the mean head circumference of the group was on the 50th centile. Motor milestone delay was usual, the cohort having a mean age of sitting unsupported of 10 months and walking of 21 months. Abnormal vision (94%) and hearing (40%) were frequent findings, but 89% of the group were attending normal primary or secondary schools. Other associations included undescended testicles (77%), hepatosplenomegaly (50%), and evidence of abnormal bleeding (56%). The mean age at diagnosis of Noonan syndrome in this group was 9·0 years. Earlier diagnosis of this common condition would aid both clinical management and genetic counselling.

Nine patients with a characteristic facies, valvular pulmonary stenosis, and short stature were first reported by Dr Jacqueline Noonan in 1963.[1] Her subsequent paper described 19 patients (12 males and seven females) with a typical facies, congenital heart disease, and clinical features of Turner's syndrome with normal chromosomes.[2] These papers ended an era of confused terminology surrounding the individual with a Turner phenotype. Turner originally reported a series of older women with webbed neck, short stature, cubitus valgus, and sexual infantilism in 1938.[3] Ullrich had independently recognised both males and females with a similar phenotype which he named status Bonnevie Ullrich, after Bonnevie's work on mice.[4] It was only after Ford *et al* had identified the karyotype 45X in a patient with the diagnosis of Turner's syndrome that a clear division was made between Turner's syndrome (45X, female only) and Noonan syndrome (normal karyotype, equal sex incidence).[5] Considerable differences between the two disorders are now well documented.

Recent excellent reviews of Noonan syndrome have been produced and have commented on areas of limited knowledge.[6 7] These included difficulty in making the clinical diagnosis, the lack of a diagnostic biochemical marker, no clear advice about management or outcome, and the absence of simple recurrence risks in genetic counselling. This study was undertaken in an attempt to answer some of these questions. A further aim was to identify pedigrees suitable for linkage analysis, in an attempt to map the gene for Noonan syndrome.

Methods

Consultant paediatricians, paediatric cardiologists, and clinical geneticists in the UK were contacted and asked for names of patients under their care with Noonan syndrome. Permission to approach over 400 individuals was obtained. The first 200 patients ascertained were then contacted and invited to participate in the research. If the family was willing to help with the project, all first degree relatives were asked to visit St George's Hospital for one day. Travelling expenses were paid if necessary in an attempt to remove a social class bias. The ascertained proband and all first degree relatives underwent a standardised symptom review and clinical examination. Echocardiography and clinical photography were performed on all the family members. Blood was taken for DNA studies. Further specific examinations were performed on different cohorts during the project. These included abdominal ultrasound, orthoptic and ophthalmological examination, coagulation studies, and speech therapy assessment.

Results

A clinical diagnosis of Noonan syndrome was made in a total of 151 individuals (83 males and 68 females) derived from 123 families. The age range of the patients was from one week to 60 years (mean 12·6 years). Data were obtained from family questionnaires, clinical examination, and specific investigations.

OBSTETRIC DATA

The mean gestational age at delivery was 39 weeks. A clinical diagnosis of polyhydramnios had been made in 43 of the 130 pregnancies whose obstetric details were available (33%). The mode of delivery had been ascertained in 149 pregnancies. A normal vaginal delivery occurred in 103 cases (69%), a forceps delivery was performed in 13 cases (9%), and a caesarean section in 32 cases (21%). The birth weight was available for 114 babies born at term (38–42 weeks) and had a mean (SD) of 3450 (510) g. The majority of parents had recognised that their baby was generally oedematous at birth, and lost excessive weight over the first week of life, but this was not possible to quantify.

CARDIAC DATA

Corrective cardiac surgery had been performed on 31 individuals at the time of the project. All 151 probands had echocardiograms performed. The following data are also derived from echocardiograms performed by regional cardiac units before corrective surgery. Pulmonary stenosis was detected in 93 cases (62%) and was usually due to a dysplastic pulmonary valve. The pulmonary stenosis was an isolated lesion in 65 cases (43%), associated with an atrial, ventricular, or atrioventricular septal defect in 20 cases (13%), and with hypertrophic cardiomyopathy in a further eight cases (6%). Hypertrophic cardiomyopathy, including asymmetrical septal hypertrophy, was present in 20% of the study group. It was found as an isolated lesion in 19 cases (13%), and in two cases was associated with a patent ductus arteriosus. Three children had undergone surgical myomectomy, and two further children had required cardiac transplantation for severe heart failure in infancy. Other cardiac findings included isolated septal defects (nine cases) and mitral valve prolapse (four cases). Only 19 individuals (12·5%) had normal echocardiograms.

FACIAL CHANGES

The predominant facial features of Noonan syndrome seen in this group were hypertelorism, down slanting palpebral fissures with high arched eyebrows, epicanthic folds, full upper lip, depressed nasal root with a wide nasal base, and low set ears with a thickened helix. Severe ptosis (either unilateral or bilateral) was present in 63 individuals (42%). Obvious webbing of the skin of the neck (excluding the common apparent neck shortening) was present in only 34 cases (23%). The characteristic facial changes of children with Noonan syndrome at varying ages are demonstrated in fig 1, 2, and 3.

FEEDING DIFFICULTIES

Feeding histories were obtained in 144 cases. There were no significant feeding difficulties in 35 cases (24%). Mild feeding problems (defined as the infant having a poor suck, with each feed taking on average over an hour to complete) were reported in 21 cases (15%). Moderate feeding difficulties (defined as a very poor suck, with slow feeding and recurrent vomiting with most feeds) were reported in 54 cases (38%). Severe feeding problems (defined as requiring tube feeding for two weeks or longer in a term infant) were found in 34 cases (24%).

DEVELOPMENTAL DATA

The age at which the child first sat unsupported was known in 126 cases, and had a mean (SD) age of 10 (4·5) months. The time of first walking unsupported was available for 112 cases, and had a mean (SD) age of 21 (10·2) months. The age at which the child could first talk in simple two word sentences was known in 102 children, and had a mean (SD) age of 31 (9·6) months.

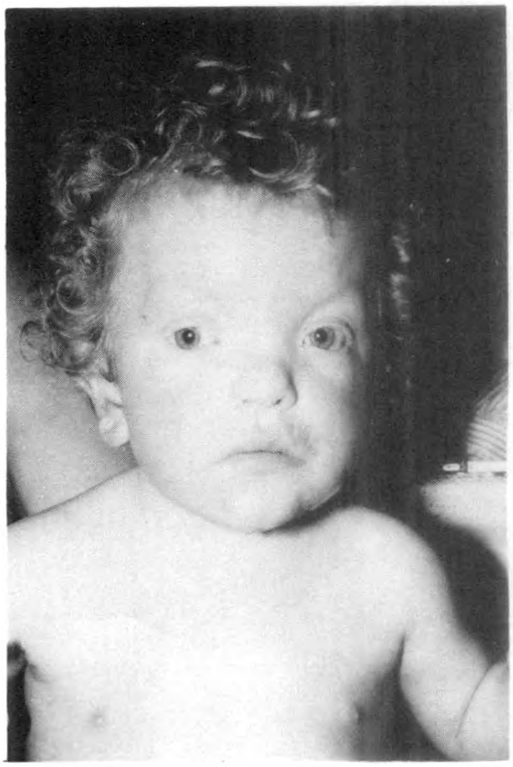

Figure 1 *Child with Noonan syndrome aged 2 years.*

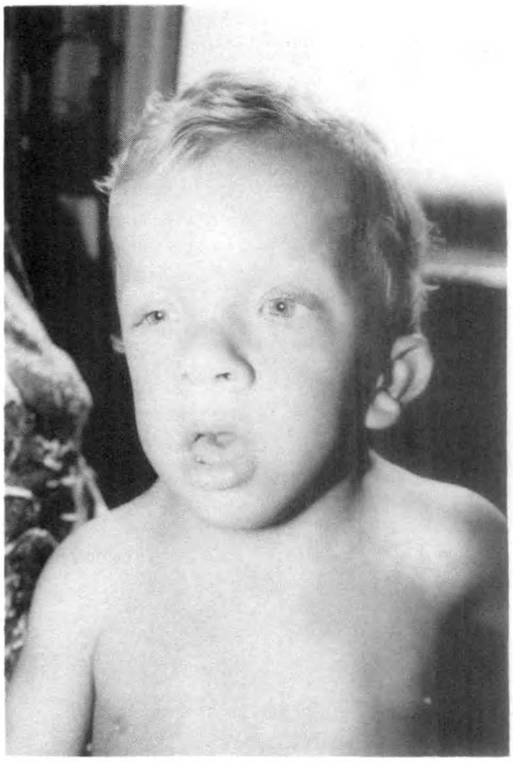

Figure 2 *Child with Noonan syndrome aged 4 years.*

Hearing tests had been performed on 146 of the group and hearing loss was reported in 58 (40%). In the great majority this was due to

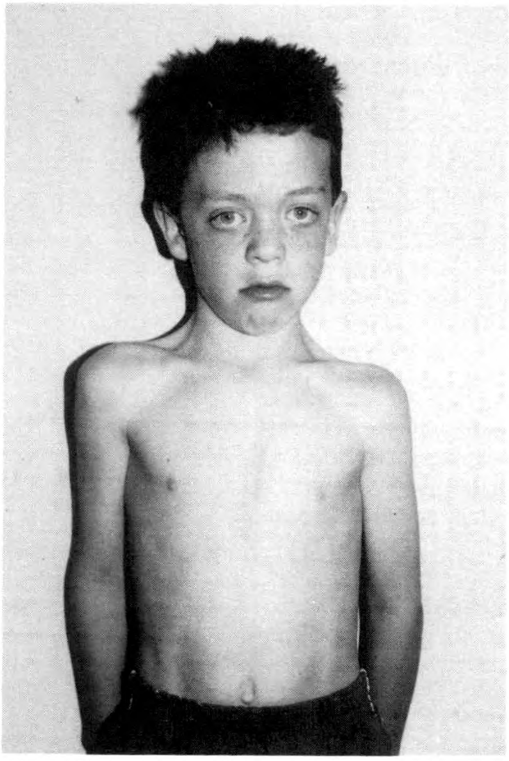

Figure 3 *Child with Noonan syndrome aged 8 years.*

serous otitis media. Nerve deafness requiring hearing aids had been detected in five children (3%).

Tests of vision had been performed on 145 individuals. These were reported as abnormal in 80 (55%). Because of this high figure, a cohort of 52 consecutive individuals underwent full orthoptic and ophthalmological evaluation during the study day. Strabismus was detected in 33 (63%) with 16 (31%) demonstrating amblyopia. Significant refractive errors (both myopia and hypermetropia) were present in 35 (67%). Only three (6%) of the cohort had a normal eye examination.

One hundred individuals were of school age or older. Of these, 84 individuals either were attending or had attended a normal primary or secondary school. A further five children attended a school for the physically handicapped. Only 11 children required schooling at a school for the educationally subnormal (11%).

GROWTH

The height, weight, and head circumference data were compared with normal centiles. The data were plotted on Tanner and Whitehouse charts and the closest centile was recorded. The results are shown for height (fig 4), weight (fig 5), and head circumference (fig 6). Twelve of the study population were receiving biosynthetic growth hormone treatment at the time of the study, and growth data was utilised from before the treatment was commenced. Bone age (measured by the standard Greulich and Pyle method) was assessed in 37 cases. The mean (SD) delay of the bone age behind chronological age was 2·0 (1·36) years.

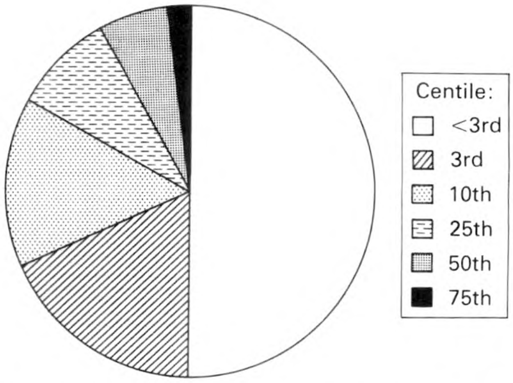

Figure 4 *Height compared with normal centiles: percentage of total group.*

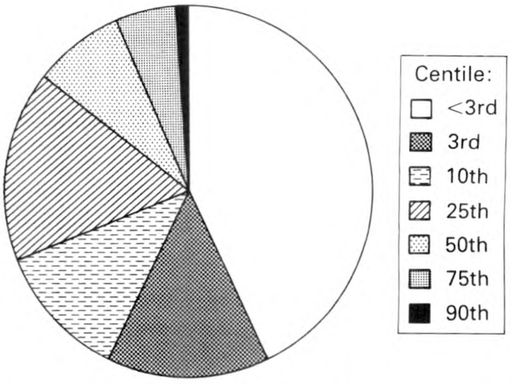

Figure 5 *Weight compared with normal centiles: percentage of total group.*

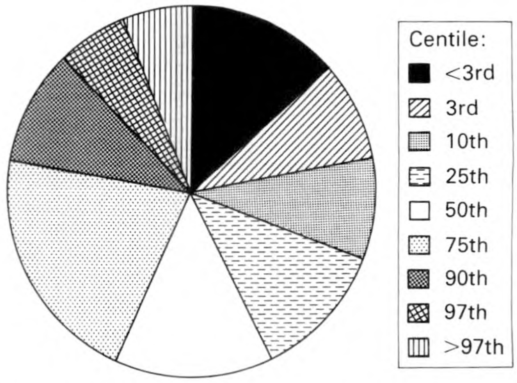

Figure 6 *Head circumference compared with normal centiles: percentage of total group.*

Undescended testicles were detected in 64 out of 83 males (77%). Puberty was delayed in both sexes. The mean (SD) age of menarche in 20 women was 14·6 (1·17) years. In the men puberty was reported as being significantly delayed and prolonged, but accurate data were not available retrospectively.

HISTORY OF BLEEDING

Easy bruising and bleeding were frequently reported by the study group. Bleeding histories were defined as normal, mild, moderate, or severely abnormal. Mildly abnormal bleeding was defined as easy bruising, with raised bruises >5 cm in diameter occurring over the whole body after minor trauma. Moderately abnormal bleeding was defined as major bruising occurring after surgery (for example, orchidopexy or cardiac catherisation) or postoperative bleeding lasting for over 24 hours (for example, after dental extraction). Major abnormal bleeding was defined as a life threatening haemorrhage requiring emergency blood transfusion. A normal history was found in 63 cases (42%). A mildly abnormal history was given by 51 patients (34%), moderately abnormal by 32 patients (21%), and a severe haemorrhage had occurred in five patients (3%).

ABDOMEN

Hepatosplenomegaly unexplained by cardiac failure was a common clinical finding in the total group (26%). This was more prominent in younger children and decreased with age. There had been no case of hepatic dysfunction associated with the organomegaly. A further cohort of 45 consecutive patients subsequently underwent abdominal ultrasound examination. Significant hepatosplenomegaly was detected in 23 cases (51%) with renal abnormalities seen in only five cases (11%). In one child of monozygotic twins, abdominal ultrasound revealed a choledochal cyst. An ultrasound of the second twin was normal.

ORTHOPAEDIC ABNORMALITIES

The classical sternal change seen in Noonan syndrome (pectus carinatus superiorly and pectus excavatum inferiorly) was present in 144 out of 151 cases (95%). A thoracic scoliosis was detected in 20 individuals (13%) but in no case had this required medical or surgical treatment. Other orthopaedic abnormalities included talipes equinovarus (12%), joint contractures (4%), radioulnar synostosis (2%), and cervical spine fusion (2%).

NEUROMUSCULAR ABNORMALITIES

Significantly abnormal joint hyperextensibility was found in 75 cases (50%). Hypotonia was also a common clinical finding. Serum creatine kinase was measured in a cohort of 35 consecutive patients. All concentrations were in the normal range for age and sex, and had a mean of 60·5 IU/l.

Recurrent convulsions had occurred in 20 individuals (13%). These were grand mal seizures in 14 cases (9%), temporal lobe epilepsy in four cases (3%), and febrile convulsions in two cases (1·5%). An unexplained peripheral neuropathy leading to distal weakness and altered sensation was detected in three adults and one child. Cervical cord compression had been excluded in all cases, and investigation had failed to reveal any cause for the neurological findings.

SKIN CHANGES

A considerable range of ectodermal changes was found. Ulerythema ophryogenes is a severe follicular keratosis previously noted to be associated with Noonan syndrome.[8] It occurs predominantly on the extensor surfaces and the face, where it may lead to absent eyebrows. This particular dermatological appearance was seen in 21 cases (14%). The hair in Noonan syndrome has previously been described as either thick and curly or thin and sparse.[9] Normal hair was present in 91 cases (60%), thick and curly hair in 44 cases (29%), and sparse hair was present in 16 cases (11%). The most useful skin sign was an extra prominence on the pads of all fingers and toes (fetal pads), which was present in 101 cases (67%). Multiple lentigines (over 100 counted on the trunk) were present in five cases (3%).

OTHER ASSOCIATIONS

Abnormalities in the lymphatic system were not common, apart from minor pedal lymphoedema. One case each was documented of lymphatic dysplasia on the lip,[10] a lymphatic cyst in the neck, and pulmonary lymphangiectasia. Hypothyroidism had been documented in six cases. Antimicrosomal thyroid antibodies were measured in 23 consecutive asymptomatic cases and were positive in seven (30%). Evidence of a further autoimmune dysfunction was provided by one case each of vasculitis, vitiligo, and anterior uveitis. Evidence of a possible immunodeficiency was suggested by frequent lower respiratory infections, and one case each of a brain abscess, bacterial endocarditis, and osteomyelitis. The differences in clinical phenotype between individuals with and without an affected first degree relative were studied using χ^2 analysis of eight variables. No significant difference was observed between the two groups with respect to incidence of cardiac disease, developmental delay, epilepsy, or neck webbing. However, individuals without an affected parent with Noonan syndrome, did have a significantly increased incidence of short stature ($p<0{\cdot}01$), skeletal abnormalities ($p<0{\cdot}01$), hepatosplenomegaly ($p<0{\cdot}01$), and sparse hair ($p<0{\cdot}01$).

Discussion

The incidence of Noonan syndrome in the UK population is unknown. It may be the second commonest syndrome associated with congenital heart disease after Down's syndrome. Previous reviews have suggested an incidence of between one in 1000 and one in 2000 of the population.[6 7] Considering the frequency and importance of Noonan syndrome, surprisingly few clinical studies have been reported. A total of six complete studies have been performed, giving details on some aspects of the phenotype in 216 patients.[2 11–15]

Short stature in Noonan syndrome has been well defined on retrospective data and centile charts are available.[16 17] This study has demonstrated clearly that the growth reduction seen in Noonan syndrome is the same for both height and weight. It is interesting, however, that the head circumferences of this group were normally distributed, as macrocephaly has been reported previously.[6] The high incidence of cardiac anomalies in this group may have been due to the continued reluctance to make a diagnosis of Noonan syndrome in the absence of congenital heart disease. Pulmonary stenosis has been the commonest cardiac abnormality reported in all previous studies, with a frequency between 25–90%. Hypertrophic cardiomyopathy is increasingly recognised by echocardiography, and its frequency in this group (20%) is twice that previously reported in studies using angiography.[13] A further important point to be highlighted from this study is the low incidence of significant renal abnormalities in Noonan syndrome compared with Turner's syndrome.[18] Musculoskeletal changes have been recognised as an important component of the syndrome. However previous reports of an association between Noonan syndrome and malignant hyperpyrexia have not been confirmed in this series.[19 20] Hypotonia and hyperextensibility in the younger child probably explain much of the early delay in motor milestones. Developmental outcome in the older child does not seem to confirm earlier reports of frequent mental retardation.[2 11 12] Hopkins-Acos and Bunker made the relevant point that speech delay may be related to hearing loss in Noonan syndrome,[21] and serous otitis media was a common finding in the study group. Although specific learning disabilities have been reported in a few patients,[22 23] more detailed studies are needed.

Clinical differences were observed between apparently familial and sporadic cases of Noonan syndrome. The apparently sporadic cases seen in this study were shorter with an increased incidence of skeletal changes, hepatosplenomegaly, and sparse hair. Only one previous smaller study had reported differences between sporadic and familial cases and had noted an increased frequency of developmental delay and short stature in the familial group.[11] The most likely explanation for the clinical differences noted between the two groups in our study is selection bias, with a less severe phenotype accepted for diagnosis in familial cases. However, it is also possible that these findings may represent evidence for heterogeneity within Noonan syndrome.

DIAGNOSIS

The differential diagnosis of the child with Noonan syndrome is considerable. It is important in all cases to exclude Turner's syndrome and other chromosomal abnormalities which can mimick the Noonan syndrome phenotype, for example trisomy 8p, trisomy 22 mosaicism, and sex chromosome rearrangements.[24–26] A number of teratogens in pregnancy produce a phenotype that can overlap with Noonan syndrome and need to be specifically inquired for, particularly alcohol and primidone.[27 28] Other syndromes that combine facial changes with short stature or cardiac abnormalities may be confused with Noonan syndrome, for example William's syndrome or Aarskog's syndrome. Both of these syndromes are now well defined however,[29–32] and recognition of the full phenotype of Noonan syndrome should readily allow accurate discrimination between them. Two other syndromes have been differentiated from Noonan syndrome based on specific ectodermal changes. The association of multiple lentigines with pulmonary stenosis and deafness led to the description of leopard syndrome,[33] while an emphasis on keratotic and other skin changes led to the separation of the cardiofaciocutaneous syndrome.[34] The frequent ectodermal changes seen in our study population suggests that these two syndromes cannot at present justifiably be separated from Noonan syndrome. Two previous attempts have been made to produce a scoring system that would be helpful in making the clinical diagnosis of Noonan syndrome.[14 35] While both are useful research tools, neither have come to be widely used in clinical practice, and diagnosis still rests on clinical pattern recognition.

The average age at diagnosis of Noonan syndrome in this group was 9·0 years. The facial features of Noonan syndrome alter with age,[36] and the easiest time to make the clinical diagnosis is in early childhood. A prompt diagnosis is important not only to allow recognition of treatable associations, but also to provide genetic counselling to the family.

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Prolonged acute crying in a young child

A diagnosis of infantile colic is usually not difficult as there is a history of recurrent crying, often at a set time of day, in an otherwise well baby. The child who presents with a first episode of excessive crying poses a different diagnostic problem. It is a fairly frequent cause of presentation to hospital casualty departments and diagnosis may be difficult. A study from the Children's Hospital in Denver, Colorado (Steven R Poole, *Pediatrics* 1991;88: 450–5) gives some help in tackling this problem. Over a one year period 56 children under 2 years of age were seen in the emergency department because of the recent onset of excesssive crying without fever. Babies who stopped crying before or during examination did not have a serious cause for their crying. The diagnosis was made by physical examination in 23 of the 56 children, as a result of investigations in 11, and only at follow up in 22. In 10 the 'diagnosis' was 'idiopathic crying' and six were thought to have infantile colic. Ten had otitis media and the rest had a wide variety of final diagnoses ranging from getting too excited at a family reunion to being bitten by a brown recluse spider. The importance of detailed and complete examination of the skin and skeletal system is emphasised as is examination of the eyes. Three children had unexpected corneal abrasions and one an ocular foreign body. Three had unexpected skeletal or intracranial trauma and one a foreign body in the throat that had escaped the notice of two doctors and was discovered by a third using a laryngoscope after the child had been noticed to wince on swallowing. Only one child proved to have a urinary infection. Investigation was dictated by clinical findings with only urine microscopy and culture being 'routine'.

The child who presents with acute unexplained crying is a good test of diagnostic mettle. Those who don't settle down in the casualty department, home, or surgery, and in whom a diagnosis is not apparent after detailed examination should be admitted to hospital for continued observation until a diagnosis is made.

ARCHIVIST

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Desmopressin for bed wetting: length of treatment, vasopressin secretion, and response

J H C Evans, S R Meadow

Abstract

Fifty five children with nocturnal enuresis referred to a hospital enuresis clinic entered a controlled trial to compare the efficacy of one month and three month courses of intranasal desmopressin (Desmospray). There was no significant difference in outcome between the two groups. Overall 36% improved by at least two dry nights/week during treatment, but only five children (18%) in the one month group and three (11%) in the three month group became completely dry and only one in each group remained dry after treatment.

To determine whether nocturnal polyuria was associated with a therapeutic response to desmopressin, the nocturnal urine volume, osmolality, and vasopressin concentration were measured in desmopressin responsive enuretics, desmopressin non-responders, and non-enuretic control children. There were no significant differences between the three groups.

A three month course of desmopressin is no more effective than a one month course. Although many children will improve during treatment, only a small number become dry and most will relapse when treatment is stopped.

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In recent years, coincident with the introduction of a more convenient nasal spray (Desmospray, Ferring Pharmaceuticals), desmopressin has been prescribed frequently for children with nocturnal enuresis. Furthermore, as the United Kingdom product licence has recently been extended to allow up to three months of continuous use, it is likely that longer courses of treatment will be prescribed more often.

Although there have been studies comparing desmopressin with placebo[1–3] they do not help the clinician decide on duration of treatment or selection of patients. This study, therefore, addressed two issues relating to the use of desmopressin for enuresis. The first issue was whether prolonging the duration of treatment from one month (the previous product licence limit) to three months improved either the short term or long term response. The second issue was whether nocturnal polyuria could be used to predict response to treatment. Previous studies have suggested that some children with nocturnal enuresis have lower nocturnal secretion of arginine vasopressin (AVP) than controls and consequently a larger nocturnal urine output.[4 5] It is possible that these are the children most likely to benefit from the antidiuretic action of desmopressin, and thus it should be possible to identify those likely to respond favourably to desmopressin.

The aims of this controlled study were to compare the efficacy of a one month and a three month course of desmopressin, and to determine whether diminished AVP secretion and increased urine output at night before treatment were associated with a therapeutic outcome.

Subjects and methods

THERAPEUTIC TRIAL

The trial was conducted in healthy children aged between 5 and 16 years who were wetting the bed at least two nights a week and who had been referred by general practitioners, community medical officers, urologists, or paediatricians to the enuresis clinic situated in a hospital paediatric outpatient department. Children were excluded from the trial if they were taking medications, such as salbutamol, that might cause a diuresis, or if they had had a urinary tract infection during the previous two weeks.

At the first visit a full history was taken, including inquiry about factors known to influence the outcome of treatment for enuresis such as housing problems (no indoor toilet, shared bedroom) and family difficulties (single parent, father in prison, marital discord, parental mental illness),[6] while behavioural abnormalities were assessed by scoring a Rutter A2 questionnaire.[7] A physical examination was performed, including a urine check for infection.

Bed wetting was documented by the children (aided by their parents) keeping a written record of wet and dry nights. During the trial no other treatment was allowed and the parents were asked not to restrict fluids or 'lift' their child to the toilet when they themselves went to bed.

A four week baseline observation period was undertaken after which the children were assigned to either one month or three months of treatment and then followed up for four weeks off all treatment. Children in the three month group were assessed after eight weeks of treatment; if no improvement was detected, alternative treatment was started. Desmopressin nasal spray (Desmospray) was prescribed initially in a dose of 20 μg but increased to 40 μg if there were any wet nights after the first three nights of use. The parent and child were asked to administer the spray in the half hour before retiring to bed. They received verbal and written instruction on how to administer the spray and this was demonstrated by the doctor using a placebo spray (supplied by Ferring Pharmaceuticals).

Children were given desmopressin for one month or three months according to a system of quota allocation,[8] which enabled the groups to be matched for Rutter A2 score, family or social problems, adverse housing, allergic rhinitis, age, severity, sex, the presence of diurnal wetting, and previous treatment for enuresis.

Therapeutic outcome was assessed by comparing the number of dry nights/week in the two groups before treatment, in the last two weeks of treatment, and in the last two weeks of follow up.

AVP STUDY

Urinary AVP excretion, urinary osmolality and nocturnal urine output were studied in children with enuresis and in non-enuretic control children. The enuretic children were studied before entering the therapeutic trial of desmopressin and were subsequently classified as either desmopressin responsive (improved by two or more dry nights/week during treatment) or treatment failures (no better or worse during treatment). Control subjects were enlisted from the healthy, non-enuretic siblings of children attending the general paediatric outpatient clinic with conditions other than enuresis.

Children were admitted to hospital for one night for assessment of nocturnal urine output and AVP excretion. After emptying their bladder before going to bed, urine was collected by waking the child every two hours to void until and including the urine voided immediately on rising in the morning.

Urine was collected into sterile containers and at the end of the collection the volume was measured and the sample well mixed before taking a 20 ml aliquot which was stored at −20°C for later analysis.

Urinary AVP concentrations were measured in duplicate by radioimmunoassay, using specific antiserum raised in rabbits, against AVP (Vasopressin Arginine Radioimmunoassay Kit, Diagnostic Systems Laboratories); the lower limit of detection of AVP was 10^{-3} pg/l, and the coefficient of variation for the assay was between 5·6 and 10·5%. Urinary creatinine concentration was measured by the Jaffé reaction, and urine osmolality was measured from the freezing point depression using an automated micro-osmometer (Hermann Roebling, Berling). Results were expressed as AVP:creatinine ratio.

The stability of AVP in urine was assessed by comparing the measured concentration of AVP in urine in a control sample that was stored at −20°C immediately after voiding, a method of storage that does not affect the recovery of AVP from urine,[9] with an aliquot of the same urine incubated at room temperature for 24 hours and with a further aliquot incubated at 37°C for 24 hours. The samples were each assayed five times in parallel.

STATISTICAL METHODS

Analysis of results was undertaken using the Statgraphics computer software package (STSC Inc).

In the therapeutic trial, comparison of the incidence of factors in the two groups was assessed by the χ^2 test. The change in the mean number of dry nights between the start and end of treatment was compared between the two groups using the unpaired *t* test with appropriately constructed confidence intervals; and the number of responders in the two groups compared using the χ^2 test (for this purpose a 'response' was defined as an improvement of two or more dry nights/week and children withdrawn from the trial were considered non-responders). In addition, the number of children who were completely dry in the two groups was compared using either the χ^2 or Fisher's exact test.

In the urinary AVP study nocturnal urinary AVP:creatinine ratio, urine osmolality, and the nocturnal urine output were compared between three groups (controls, enuretic desmopressin responders, and enuretic treatment failures) using one way analysis of variance. The data were positively skewed and therefore log transformed for analysis, results being expressed in the original units using the geometric mean and the interquartile range.

The study received approval from the Leeds Eastern Health Authority ethics committee.

Results

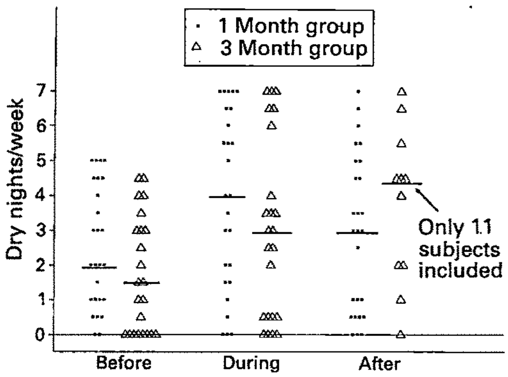
Fifty five children were studied, 28 were assigned to one month of treatment and 27 to three months, using the quota allocation system. There were no significant differences between the two groups for the incidence of the characteristics shown in table 1 (χ^2 <0·7, 1 df, p>0·2 in each case). The median age was 10 years (range 5–16 in the one month group and 10·8 years (range 6–16) in the three month group.

Six children failed to complete the trial: two from the one month group and four in the three month group. One child developed chest pain and wheezing and stopped treatment on the advice of his general practitioner, five children failed to improve during treatment and the parents either stopped treatment early (n=2), lifted the child during the night (n=2), or failed to attend follow up appointments (n=1). Twelve children in the three month group failed to improve after eight weeks of treatment and were given alternative therapy.

The figure demonstrates the number of dry nights/week in the two groups, before, during, and after treatment. In the one month group the median number of dry nights/week increased

Table 1 Characteristics of children allocated to either one month or three months of desmopressin, and the number showing these characteristics

	1 Month (n=28)	*3 Months (n=27)*
Previous treatment for enuresis	19	19
Male subject	17	17
Dry ≤2 nights/week	15	17
Adverse family or social factors	10	11
Rutter A2 score ≥18	9	8
Age <8 years	9	7
Adverse housing	9	6
Diurnal symptoms	8	7
Allergic rhinitis	1	1



The number of dry nights/week in children receiving treatment with either one month or three months of desmopressin. Median values represented by a bar.

from two to four with treatment, and declined to three nights/week after treatment. In the three months group the median values increased from 1·5 to three with treatment; follow up data were only available on a subgroup off 11 subjects who had responded to treatment and the median value for these subjects was 4·5 dry nights/week. The mean change (SD) in the number of dry nights/week with treatment was +1·4 (1·7) in the one month group and +1·3 in the three month group. The difference in the two group means was 0·1 nights/week (95% confidence interval −1·1 to +0·8, p=0·75).

There were no significant differences in the proportion of responders in the two groups either during treatment or after treatment (table 2). Overall 20 children (36%) improved with treatment and 11 (20%) remained so one month after treatment was completed. Only five children in the one month group (18%) and three children in the three month group (11%) became completely dry on treatment, and this difference was not significant (Fisher's exact test p=0·47). One in each group remained dry off treatment.

The measured concentration of AVP in urine incubated for 24 hours at room temperature (22°C) or at 37°C was 96% and 87%, respectively, of the control sample, which had been stored at −20°C.

Table 2 The number of responders in the one month and three month treatment groups*

	1 Month (n=28)	*3 Months (n=27)*	
During treatment	12	8	(χ^2 0·5, p=0·46)
After treatment	6	5	(χ^2 0·07, p=1)

*Response defined as improvement by ≥2 dry nights/week.

Urine collections were obtained from eight enuretics with a median age of 12 years (range 7–18) who were subsequently classified as desmopressin responders, from 10 enuretics with a median age of 9 years (range 5–12) who were treatment failures, and from eight non-enuretic controls with median age 10·5 years (range 6–15). The urine volumes, osmolalities, and AVP concentrations in the three groups are shown in table 3. There were no significant differences between groups for any of these parameters.

Discussion

Nocturnal enuresis is a common childhood problem, which in the majority of children can be managed successfully using behavioural treatments such as enuresis alarms. However, for some children drug treatments may be needed. When drugs are used it is logical to use the dosage and treatment regimen associated with maximum benefit. Desmopressin, an antidiuretic agent, is one of the few drugs effective in the treatment of nocturnal enuresis. Although most early studies used a dose of 10–20 μg,[3 10 11] there is now good evidence that increasing the dose up to 40 μg results in a higher response rate.[5] Unfortunately, it also increases the expense of treatment. In order to justify the routine use of a three month course of desmopressin it would be necessary to demonstrate a substantially greater response than with shorter treatments. There are no published studies comparing different durations of treatment with desmopressin, though uncontrolled trials suggest that it remains effective when prescribed for months or even years[12 13] and one study found no difference in the number of dry nights in the first and last two weeks of treatment.[2]

Our study did not demonstrate any difference between one month and three months of treatment in the proportion of children dry or improved, either during treatment or when reviewed four weeks after the end of treatment. Overall, 36% appeared to benefit from treatment with 15% dry and a further 21% improved, while off treatment 4% (two patients) were dry and a further 16% improved. Direct comparison with previous publications is difficult because of the variety of dosages used, the variety of populations and age ranges studied and because of the different methods chosen to describe outcome. Controlled trials have shown that

Table 3 The urinary data of enuretics who responded or failed to respond to desmopressin, and in non-enuretic controls

	Responders (n=8)	*Non-responders (n=10)*	*Controls (n=8)*	
Nocturnal urine volume (ml)				
Geometric mean	345	265	221	F ratio 1·5
Range	193–620	140–800	93–510	p=0·23
Nocturnal urinary osmolality (mmol/kg)				
Geometric mean	506	578	703	F ratio 1·2
Range	285–1053	243–1113	348–1069	p=0·32
Nocturnal urinary AVP concentration (pg/mmol creatinine)				
Geometric mean	0·9	2·8	2·6	F ratio 2·0
Range	0·2–3·9	0·7–10·8	0·5–16·8	p=0·15

between 12% and 70% become dry during treatment[1 3 5 11] while 41%–88% are perceived to improve significantly.[1 3 10] The proportion who are dry after treatment stops varies between 0 and 31%.[1 3 13] By comparison, our response rates are low. One possible explanation for this is the high proportion of children with refractory enuresis (69%), although in many cases the initial treatment was only a short trial of imipramine with little or no supervision. Dimson in a study of refractory enuretics found similarly poor results with 12% dry, 41% improved, and 0% dry after treatment.[3]

Nocturnal polyuria has long been considered as a possible contributory factor in the pathogenesis of enuresis.[14] It is known that healthy adults and children exhibit an appreciable diurnal variation in urine output,[5 15] which diminishes during the night irrespective of whether the individual sleeps or refrains from drinking during the night, and that the probable explanation for this is the presence of a diurnal variation of AVP release with an increase in plasma AVP concentration during the night.[5 16] Early studies of night time urine production have produced conflicting results in children, Poulton and Hinden found that the majority of enuretic children did have nocturnal polyuria, but a detailed study by Vulliamy showed similar urine outputs in enuretic children and non-enuretic controls (with the physiological diurnal variation present in both groups).[14 17] Recent studies of children aged 11–17 years with and without enuresis, receiving a strictly controlled fluid intake, have shown a significant blunting of the diurnal rhythm in plasma AVP, with either very little or no increase in the night time concentration in the enuretic children, and that this is associated with a loss of the diurnal rhythm of urine output, with enuretics not exhibiting the expected reduction in nocturnal urine production.[4 5]

It is tempting to speculate that those children with nocturnal polyuria secondary to AVP deficiency are the ones most likely to benefit from desmopressin. Dimson found that children who concentrated their urine (increasing the early morning urinary osmolality to >1000 mmol/kg) after desmopressin had the best clinical response, but also showed that those who already had a high early morning urinary osmolality responded well.[3]

Our study of nocturnal urine output, urinary vasopressin concentration, and urine osmolality did not demonstrate a significant difference between control children, enuretics who did not respond to desmopressin, and enuretics who did respond to desmopressin. There was, however, a trend towards the desmopressin responsive enuretics having lower AVP concentrations and larger volumes of dilute urine at night, with the (geometric) mean urine volume highest in the responders and lowest in the controls, while the AVP concentrations were lowest in the responders, intermediate in the non-responders, and highest in controls. This trend was small compared with the wide range of values seen in each group.

We elected to study urinary AVP concentrations (rather than plasma) for a number of reasons: it avoids the need for venepuncture; urinary AVP concentrations have been shown to have a consistent relationship with plasma concentrations in children[18]; and as plasma AVP has a half life of only a few minutes, urine collection may provide a more reliable assessment of AVP secretion over a period of time than intermittent venous sampling which may miss significant peaks.

There are a number of methodological factors that might explain the contrasting results between our study and that of Rittig *et al.*[5] Firstly, Rittig *et al* studied only older children whereas we included children as young as 6 years; it is possible that the diurnal variations in AVP are less well developed in younger children. Secondly, Rittig *et al* studied children under conditions of fluid restriction, which may allow identification of minor abnormalities of AVP production that are not apparent when children receive a normal fluid intake and which, more importantly, do not result in a significant change in urine output at night.

We conclude that, although there may be some abnormality in the diurnal rhythm of AVP release in children with nocturnal enuresis, when they are allowed a free fluid intake it does not result in a significant increase in night time urine production nor is it a major determinant of therapeutic response to desmopressin.

Desmopressin is a useful treatment for some children with nocturnal enuresis. Although it produces some benefit for many children, few of those children become completely dry, and most relapse once the treatment is stopped. A three month course of treatment does not increase the response rate or decrease the relapse rate when compared with a one month course in children referred to the hospital outpatient clinic. Measurement of nocturnal urine volume, osmolality, and AVP concentration does not identify clearly those who will respond to desmopressin. As improvement is seen early in treatment, responders can be identified by a short therapeutic trial and continued use reserved for those who are benefiting from treatment.

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Water intoxication

'For every action there is an equal and opposite reaction'. Twenty years ago severe hypernatraemic dehydration was common but after the introduction of low solute milks in the mid-1970s it became rare. Now there is concern in the United States about an apparent increase in severe acute hyponatraemia in babies of poor inner city families some of which may be attributable to the introduction of the low solute milks.[1] As hyponatraemia is much less likely than hypernatraemia to give rise to serious sequelae the exchange seems to be a fair one though the problem of hyponatraemia needs to be tackled by public education.

A report from the Children's Hospital of St Louis, Missouri (James P Keating and colleagues, *American Journal of Diseases of Children* 1991;**145**:985–90) gives details of 31 infants with water intoxication seen between 1975 and 1990, 22 of whom had been seen in the last three years. Quite why this sudden increase occurred in 1988 is not well explained. Fourteen of the 31 babies were girls and their ages ranged from 1 to 10 months. They all presented to hospital after the sudden onset of apnoea or convulsions. Although these are attributed to cerebral oedema, bulging of the fontanelle was 'notably absent' and neither plain radiographs of the skull nor computed tomograms showed evidence of raised intracranial pressure or cerebral oedema. All but four of the babies had a serum sodium of less than 120 mmol/l at the time of admission (range 111–127 mmol/l). They had been given excess water, usually as tap water but sometimes as dilute formula, over a period of two to eight hours at a rate of about 7·5 l/m^2 of body surface area/day (around 300 ml/kg day) shortly before admission. They came from an inner city area of very high social deprivation. Sixteen had been given water because they had 'run out of formula', four because of diarrhoea, and the remaining 11 for a variety of reasons including irritability, apparent thirst, and hot weather. They were treated by either rapid infusion of hypertonic saline or slow infusion of an isotonic solution and all recovered completely. Dr Finberg in his editorial advises against the use of hypertonic solutions.[1]

Water intoxication does not seem to have been a problem in Britain so far. There have been two reports in this journal, from Israel[2] and Thailand.[3] The reasons behind the American outbreak are unclear. Why should parents suddenly begin to poison their babies with water? There must be something we don't know about. So often we seem to prepare ourselves for the eastward spread of an American problem and it doesn't happen but a little prophylactic education about the potential danger of excessive water administration might not be a bad thing.

ARCHIVIST

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Twin peaks, extramarital conceptions, and virgin births: is there a connection?

M Murphy, V Seagroatt

Abstract

The trends in British twin and higher multiple birth rates inside and outside marriage from 1938 to 1989 were reviewed for evidence of the probable impact of the use of ovulatory stimulants.

After adjustment for maternal age monozygotic twin rates within marriage rose to a significant excess (of 12%) over those outside during the last two decades; a similar increase of higher multiple births within marriage to a significant excess (of 50%) over those outside was also seen for 1980–9. The dizygotic twin rate within marriage exceeded that outside in 1989 for only the second time in 50 years, as the difference in rates narrowed in the last decade.

It is concluded that ovulation induction and techniques of assisted conception are apparently more available to the married, with a stronger effect on higher multiple birth rates than on dizygotic twin rates. Monozygotic twin trends support the suggestion that part of the infertility treatment regimen also promotes zygote splitting.

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The profound fall in dizygotic twinning rates observed since the 1950s/60s in many developed countries taught us little about the factors that caused the decline,[1] but the recent upturn may reveal more.[2] It has been suggested that the movement of dizygotic twinning rates may, among other things, reflect change in the average fecundability of the population reproducing.[3–5] However, it may be the treatment of infertility with ovulation induction drugs that is currently most influencing the twinning rate and arresting the previous fall, so that 'natural' reproductive ability might still be in decline for reasons that remain unexplained.[6 7] Recently attention has focused on the availability of infertility treatment/assisted conception techniques for single women.[8] If such treatments are differentially available by marital status, in Britain, the situation constitutes a 'natural experiment' that may assist interpretation of the changing patterns of dizygotic twinning in particular. We therefore compared statistics on twinning and higher multiple birth rates within and outside marriage for evidence of discrepant trends, as the rates outside marriage may more accurately reflect any underlying trend in fecundability on which is superimposed the effects of infertility treatment.

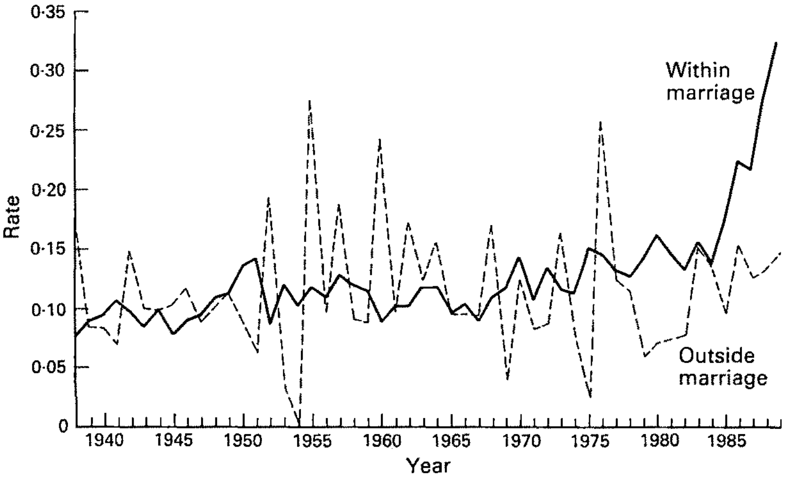

Figure 1 Age standardised triplet and higher rate of multiple births/1000 maternities: England and Wales 1938–89.

Methods

Total maternities, numbers of live and stillborn twins by sex combination, and numbers of triplet and higher order births for England and Wales were obtained by mother's age and marital status from the Office of Population Censuses and Surveys (OPCS) FM1 fertility series publications from 1974–88, except for the year 1981, when the registrars' dispute meant multiple birth statistics are inaccurate, and for 1938–73 from the Registrar General's annual reports. OPCS also made available similar data for 1989 and for twins and maternities where the birth was outside marriage but either jointly registered by both parents or by the mother alone between 1974–89. For Scotland data for twins from 1952–89 were obtained from the Registrar General's reports and directly from the General Registry Office (Scotland). These rates were age standardised and the proportions of twins which were monozygotic or dizygotic were estimated using Weinberg's rule.[9]

Results

Figure 1 shows triplet and higher multiple birth rates inside and outside marriage from 1938–89, indirectly age standardised using average rates for all women over the whole period as standard. The rates within marriage were initially constant but have increased over the last 20 years, accelerating rapidly in the 1980s, whereas the rates outside marriage do not show this increase.

Figure 2 shows total, monozygotic, and dizygotic twinning rates within and outside marriage from 1938–89 in England and Wales, indirectly age standardised using the maternal age specific unlike sexed and total twinning rates among all women for 1970 as standard. Overall, the upturn in twinning rates in the recent past is due to the reversal of the downward trend in dizygotic and the small but longstanding increase in monozygotic twin rates. Within and outside marriage monozygotic twin rates share a similar upward trajectory until the 1970s when a greater increase was seen within marriage (as for the higher order births). Dizygotic rates were consistently higher outside marriage until 1989 when they reversed. This convergence was due to the rates increasing within marriage. Figure 3 shows that Scotland has had similar but generally higher total twinning rates than England and Wales (age adjusted to the same standard) and that the rates fell there more dramatically before increasing again.

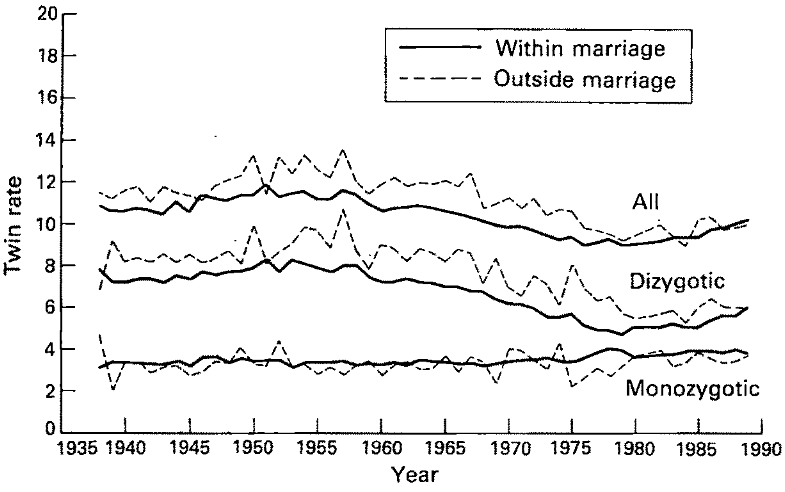

Figure 2 Age standardised twin rates/1000 maternities: England and Wales 1938–89.

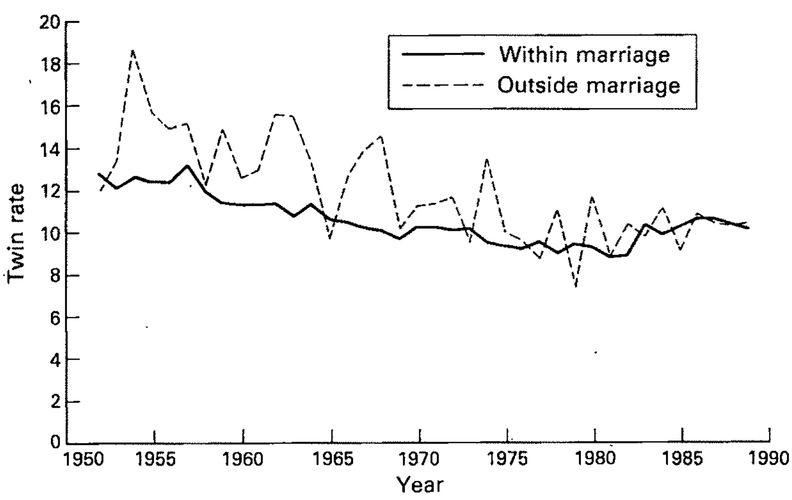

Figure 3 Age standardised twin rates/1000 maternities: Scotland 1952–89.

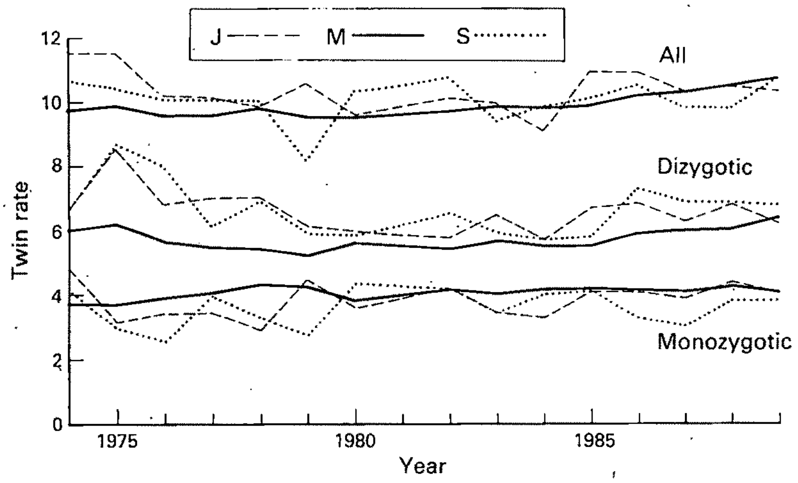

Figure 4 Age standardised twin rates/1000 maternities for all twins, monozygotic and dizygotic twins, within marriage (M) and sole (S) or jointly (J) registered maternities outside marriage: England and Wales 1974–89.

Figure 4 shows the total, dizygotic, and monozygotic twinning rates from 1974–89 for births within marriage, births outside marriage jointly registered by both parents, and those registered solely by the mother, indirectly age standardised using the average rates for all women over the whole period as standard. The proportion of births outside marriage has risen steeply over the last decade, largely accounted for by the increase in births jointly registered by both parents. In 1989, 75% of births outside marriage were jointly registered and 75% of these parents gave the same usual address, so that births outside marriage increasingly resemble those within. The rates for joint and solely registered dizygotic (and all) twins were similar, and both were higher than the rates within marriage. For monozygotic twins the jointly registered rates lay between those for the married and the solely registered. Significant differences between the sole and jointly registered twin rates were found only for the monozygotic, ($\chi^2=5{\cdot}3$; df=1, $p<0{\cdot}05$).

The table shows how the relationship between dizygotic, monozygotic, total twin, and higher order birth rates changed within and outside marriage over the five decades. For dizygotic twins the difference between the rates within and outside marriage was narrower in 1980–9 than over the previous 40 years. Monozygotic twin rates within marriage have become significantly greater than those outside over the last two decades, a pattern which is also evident in the period 1980–9 for higher multiple births.

Discussion

As far as can be judged, the evidence provided by births (which exclude ‘vanishing twins’, pregnancy miscarriage, and therapeutic abortion) should be taken at face value as an indicator of changing patterns of multiple pregnancies.

The steady increase in higher multiple births within marriage, dating from the early 1970s, seems likely to have been due to rare consequences of the use of ovulation induction agents, followed by a much accelerated increase in the mid-1980s as a more common result of the use of in vitro fertilisation and related techniques. The absolute number of these births remains small so estimation of zygosity is not warranted. The number outside marriage is so small that no definitive conclusions as to the trends can be drawn, though it would seem they have been largely unaffected by the spreading use of techniques of assisted conception.

The phenomenon that dizygotic twinning

Age standardised rates/1000 maternities for twins and higher order births by marital state and time period. Odds ratios (OR) are adjusted for age and are given with their 95% confidence intervals (CI)

Period	*Marital status*	*Dizygotic twins*			*Monozygotic twins*			*All twins*			*Higher order births*		
		Rate	*OR*	*95% CI*	*Rate*	*OR*	*95% CI*	*Rate*	*OR*	*95% CI*	*Rate*	*OR*	*95% CI*
1938–49	Married	8·0	1·0		3·5	1·0		11·5	1·0		0·10	1·0	
	Unmarried	8·9	1·13*	1·09 to 1·16	3·4	0·98	0·93 to 1·04	12·2	1·06*	1·03 to 1·09	0·10	1·09	0·81 to 1·48
1950–59	Married	8·6	1·0		3·5	1·0		12·2	1·0		0·12	1·0	
	Unmarried	9·9	1·16*	1·12 to 1·20	3·5	0·99	0·93 to 1·05	13·3	1·10*	1·07 to 1·14	0·11	0·90	0·64 to 1·28
1960–69	Married	7·8	1·0		3·6	1·0		11·4	1·0		0·10	1·0	
	Unmarried	9·4	1·21*	1·17 to 1·25	3·5	0·96	0·91 to 1·00	12·7	1·12*	1·09 to 1·15	0·13	1·17	0·89 to 1·53
1970–79	Married	6·3	1·0		4·0	1·0		10·3	1·0		0·13	1·0	
	Unmarried	7·7	1·20*	1·16 to 1·25	3·6	0·94*	0·89 to 0·98	11·3	1·08*	1·05 to 1·12	0·11	0·87	0·64 to 1·17
1980–89	Married	6·1	1·0		4·3	1·0		10·4	1·0		0·19	1·0	
	Unmarried	6·9	1·12*	1·09 to 1·15	3·8	0·92*	0·89 to 0·95	10·8	1·03*	1·01 to 1·05	0·12	0·67*	0·54 to 0·83

*Denotes OR significantly different from one; in each case they were significantly different at the 1% level.

rates outside marriage have always been higher than within, at all ages except the youngest, has been observed in a number of different countries.[4 5] It has been interpreted as evidence that women prone to twins are also more fecundable, and hence more likely to become pregnant outside marriage with an accompanying higher twin rate. Thus one explanation for the declining dizygotic twin rate was that the advent of widespread oral contraceptive use masked high fecundability/twin proneness. Concomitant social changes, such as the decrease in completed family size, would tend to be associated with a decline in dizygotic twinning while others, such as postponement of the age at which childbearing is completed, would have had the opposite effect. These explanations may be inadequate however and the decrease in dizygotic twinning may have represented a worrying decline in natural fecundability, though secular fluctuations in the rate of twinning necessarily give rise to speculation about what is the natural background rate.

Social selective processes operate continuously so that cohorts of women reproducing will differ in various ways from the generations on either side, particularly when defined in terms of marriage. However, it seems unlikely that the recent convergence of dizygotic twin rates between married and unmarried reflects a differential alteration in the 'natural' propensity to twinning. Rather, the resurgence of dizygotic twinning is due to the increased risk of multiple births after ovulation induction. There is greater likelihood of use if married or intending to marry, though it is not completely clear that the proportion of twin births after use of these drugs would be alone sufficient to have reversed the decline in twinning.[6 7] The absence of a difference in the trends in dizygotic twinning rates between the 'new' type of birth outside marriage (the birth jointly registered by both parents) and the 'old' type (the birth solely registered by the mother) may reflect a wider access to infertility treatment, irrespective of marital or partnership status, than we had imagined. It probably will not be possible to tell whether a reversal of natural fecundability also took place, but we can be sure that a birth registered by the mother alone, stereotypically a single parent, is no longer presumptive evidence that conception was unassisted by artificial means.

Of equal interest are trends in the rates of monozygotic twinning. Their long term small increase does not mirror the ups and downs of dizygotic twinning and hence it seems unlikely to be an artefact of the method of estimation of their numbers. From the mid-1970s onwards monozygotic twin rates within marriage started to exceed those outside. Very little is known to affect the risk of monozygotic twinning, except perhaps age, for which we adjusted, and the possibility that some component of the assisted conception process may influence zygote splitting.[10] There may be evidence here from the increase in relation to marriage from the 1970s onwards of the higher multiple births (zygosity unknown) and monozygotic twins (zygosity estimated) that this may be so and it should be investigated further.

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Controlled study of *Pseudomonas cepacia* and *Pseudomonas maltophilia* in cystic fibrosis

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Abstract

In a retrospective study, children with cystic fibrosis who were colonised with *Pseudomonas cepacia* were compared with a control group who were colonised with *Pseudomonas maltophilia*. Out of 216 children with cystic fibrosis seen between 1983 and 1990, *P cepacia* was recovered from 13 (median age at colonisation 12·2 years) and *P maltophilia* from 23 (median age at first colonisation 6·1 years), and both organisms were recovered in five cases. With the exception of two patients with *P cepacia* in whom no other pathogens were found, all the patients with *P cepacia* or *P maltophilia* had co-colonisation with *Pseudomonas aeruginosa*. The lack of spread of *P cepacia* to siblings with cystic fibrosis, and the relative lack of inpatient contact between colonised and uncolonised patients suggest that cross infection is not the sole route whereby patients with cystic fibrosis become infected, but the possibility of cross infection cannot be excluded from our data. Three patients with *P cepacia* died, but two of these had shown appreciable respiratory deterioration before colonisation with *P cepacia*; there was no evidence of unexpected deterioration in the remainder or in the controls with *P maltophilia*. By 1990, the prevalence of *P cepacia* was 9/133 (7%) and that of *P maltophilia* was 13/133 (10%), but it was impossible to determine to what extent this increase was due to the introduction of the routine use of selective media. Further studies are required to establish whether patients with and without *P cepacia* should be segregated.

Pseudomonas cepacia is increasingly recognised as an organism that can colonise the respiratory tract of patients with cystic fibrosis, and which may act as a pathogen. The association of *P cepacia* colonisation with respiratory deterioration in some cases, and the relatively poor response to antibiotic treatment, have caused concern.[1] Anxiety has been enhanced by the possibility of cross infection between patients with cystic fibrosis.[2] In an attempt to limit such cross infection, a number of major centres (for example, the Hospital for Sick Children in Toronto; H Levison, personal communication) have recently segregated patients into groups with and without *P cepacia* colonisation, with separate clinics, isolation, or cohorting during hospitalisation, and rigorous handwashing by professionals after patient contact. Concern about the risk of social contact has led to a number of restrictions imposed by professionals and others (including patients themselves), such as the setting up of 'cepacia' or 'non-cepacia' cystic fibrosis camping holidays. It has been previously claimed in an uncontrolled study that such measures may sharply reduce the number of patients who become colonised with *P cepacia*,[3] but this has not yet been confirmed by controlled studies, and the possible mode of transmission between patients is obscure.

The microbiology laboratory at Booth Hall Children's Hospital has been storing on a microcomputer data on all bacteria isolated from sputum of patients with cystic fibrosis since 1983. This database has enabled us to perform the present study, the aim of which was to explore possible risk factors for the acquisition of *P cepacia* colonisation including cross infection. We retrospectively reviewed the clinical and microbiological records of patients with cystic fibrosis, and used as controls those who were colonised with *Pseudomonas maltophilia*, an organism which we have not hitherto regarded as a pathogen in cystic fibrosis.

Patients and methods

Between 1983 and 1990, 216 children with confirmed cystic fibrosis have attended the University Department of Child Health at Booth Hall Children's Hospital. As a standard part of our management throughout this period, all patients were instructed to send postal samples of sputum (or cough swabs in those unable to expectorate) to the microbiology laboratory at intervals of two weeks. All patients in whom *Pseudomonas aeruginosa* was recovered on two or more consecutive sputum samples were treated electively with a two week course of intravenous antipseudomonas antibiotics every three months. Initially all such treatment was given in hospital, but such patients are increasingly treated at home. Oral ciprofloxacin was avoided for such treatment because of the rapid development of resistance. During hospitalisation, sputum samples were collected daily. During the early 1980s, different species of pseudomonas were recognised by close examination of colony appearance, followed by subculture of atypical colonies on selective media. Selective media for *P cepacia* (blood agar with added ticarcillin and polymyxin B) have been used routinely for all sputum samples since 1988, and the routine use of selective media for *P maltophilia* (blood agar with added imipenem) in all samples was introduced in 1990.

The following data were sought in this

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retrospective study: age at which *P cepacia* or *P maltophilia* was first recovered; prior use of inhaled antibiotics or steroids; details of siblings with cystic fibrosis; number of prior hospital admissions; number of occasions during which a hospital inpatient known to harbour *P cepacia* or *P maltophilia* was hospitalised at the same time as a patient from whom *P cepacia* or *P maltophilia* had not been recovered but who was to become colonised with either organism within 12 months. Also sought was evidence of unexpected clinical deterioration (defined as an appreciable increase in respiratory symptoms or deterioration in lung function) coinciding with the first recovery of *P cepacia* or *P maltophilia* and the therapeutic response to the detection of either organism. Colonisation was defined as a single positive sputum culture.

Results

P cepacia was recovered from 13 and *P maltophilia* from 23 children with cystic fibrosis. Both organisms were recovered in five cases. *P cepacia* was first recovered at 0·3 to 15·1 years (median 12·2), and *P maltophilia* at 0·8 to 13·6 years (median 6·1). With the exception of two patients with *P cepacia* in whom no other pathogens were found (described below), all of the remaining patients with *P cepacia* or *P maltophilia* had co-colonisation with *P aeruginosa*. The prevalence of *P cepacia* and *P maltophilia* recovery are shown in the table. The laboratory also receives specimens from other patients with cystic fibrosis in the North West region, including adults, although these are received on a less regular or frequent basis. Data on prevalence of *P cepacia* and *P maltophilia* in all samples is included, for comparison, in the table.

SIBLINGS

Three out of 13 patients with *P cepacia* had a sibling with cystic fibrosis, as did 4/23 with *P maltophilia*. Neither *P cepacia* nor *P maltophilia* had been recovered from any of these siblings.

PREVIOUS ADMISSIONS TO HOSPITAL

The number of previous hospital admissions before the first isolation of *P cepacia* ranged from 0–19 (median 4·5), compared with 1–14 (median 5) for those with *P maltophilia*. Two highly atypical children with cystic fibrosis acquired *P cepacia* during their presenting illness. One presented at 3 months of age with chlamydia pneumonia and failure to thrive. The only bacterial pathogen ever cultured from the respiratory tract was *P cepacia*, and despite repeated courses of intravenous antibiotics, this child died at the age of 5 months. The other presented at 4 months of age with a six week history of coughing, loose stools and failure to thrive, and a three day history of worsening stridor requiring intubation after a respiratory arrest. *P cepacia* was grown from blood cultures taken on admission, but no pathogens were isolated from the respiratory tract. This child did not have sickle cell disease, a possible risk factor for *P cepacia* bacteraemia.[4] At the age of 19 months he was well, and *P cepacia* had not been cultured from him again. No patient acquired *P maltophilia* during the presenting illness.

PRIOR ADMINISTRATION OF INHALED ANTIBIOTICS

Seven of the 13 (54%) patients with *P cepacia* had received twice daily inhaled colistin before the recovery of the organism. Only four of these seven were receiving regular inhaled antibiotics at the time *P cepacia* was first recovered, and in the other three inhaled colistin had been discontinued at least six months before the first isolation of *P cepacia*.

Six of the 23 (26%) patients with *P maltophilia* had received twice daily inhaled colistin or tobramycin before recovery of the organism. Only three (colistin two, tobramycin one) of these six were receiving regular inhaled antibiotics at the time *P maltophilia* was first isolated, and in the other three (all of whom received colistin) inhaled antibiotics had been discontinued at least six months before the first isolation of *P maltophilia*. The prior use of inhaled antibiotics was not significantly different between the two groups. $\chi_1^2=2{\cdot}7$.

PRIOR ADMINISTRATION OF INHALED STEROIDS

Two out of 13 (15%) with *P cepacia* had received inhaled steroids immediately before isolation of the organism, compared with three out of 23 (13%) patients with *P maltophilia*.

HOSPITALISATION BEFORE RECOVERY OF *P CEPACIA* OR *P MALTOPHILIA*

The 13 patients with *P cepacia* had between them a total of 120 admissions before the first recovery of the organism, and on five occasions hospitalisation coincided with the presence of at least one other patient with *P cepacia* on the same ward. The 23 patients with *P maltophilia* had between them a total of 154 admissions before the first recovery of the organism, but on only one occasion did hospitalisation coincide with the presence of another patient with *P maltophilia* on the same ward.

Although the number of 'at risk' inpatient

Prevalence (%) of P cepacia and P maltophilia in respiratory tract secretions in patients with cystic fibrosis for children attending Booth Hall Chilldren's Hospital and for all samples received from patients with cystic fibrosis

	1983		*1989*		*1990*	
	Booth Hall	*All patients**	*Booth Hall*	*All patients**	*Booth Hall*	*All patients*
P cepacia	0/84 (0)	0/177 (0)	3/124 (2)	16/320 (5)	9/133 (7)	36/331 (7)
P maltophilia	0/84 (0)	0/177 (0)	9/124 (7)	27/320 (8)	13/133 (10)	52/331 (16)

*All patients regularly sending sputum samples to the laboratory, and therefore including those treated at other centres.

contacts between colonised and those to become colonised in the future was greater in the *P cepacia* group than in the *P maltophilia* control group (five *v* one occasion), in only one of the five *P cepacia* cases did a 'non-colonised' child in contact with an infected child become colonised with *P cepacia* within 12 months of the potential contact.

SUBSEQUENT EVENTS

Of the 13 children with *P cepacia*, three have died. *P cepacia* was first isolated six months before their deaths, and two of these cases were showing a considerable clinical deterioration at least 18 months before *P cepacia* was first isolated, and only in the infant described above, who developed an overwhelming infection, was *P cepacia* recovery associated with rapid deterioration. Of the remaining 10 children with *P cepacia*, the time from first isolating the organism to the present time ranges from 0·4–4·7 years (median 1·3), and only in one of these patients have we seen a progressive deterioration of clinical condition as assessed by increased sputum production, increased respiratory symptoms, and deteriorating chest radiograph changes.

Of the 23 patients with *P maltophilia*, all are alive (including the five who were also colonised with *P cepacia*, and none has shown an unexpected deterioration' in clinical condition since *P maltophilia* was isolated.

Throughout the study period, our unit has pursued an active policy of regular intravenous anti-*P aeruginosa* antibiotic treatment every three months in all patients from whom the organism can be regularly recovered. Our policy has always been to discontinue regular intravenous or inhaled antibiotics once *P cepacia* has been recovered, and avoid intravenous antibiotics unless there was an appreciable respiratory deterioration, in the hope that the cessation of such treatment might be associated with disappearance of *P cepacia* and recolonisation with *P aeruginosa*. In three of the 13 patients with *P cepacia*, the organism ceased to be recoverable from the sputum, and has not been recovered for at least 18 months after the first isolation.

Discussion

This report highlights some of the drawbacks of any retrospective study, and there are a number of methodological drawbacks. The patients are a highly selected and therefore atypical group who have attended a cystic fibrosis centre, and thus over represent complex or severe cases and those with particularly well motivated families who are willing to travel large distances for medical supervision. Our examination of acquisition of *P cepacia* or *P maltophilia* by cross infection has had to be confined to what may pose the greatest but by no means the sole means of cross infection, namely hospitalisation. The retrospective nature of the study has prevented us from examining other important potential contacts between colonised and non-colonised patients, such as in the outpatient department, the physiotherapy department, hospital organised day trips or social contacts between patients. We have no data on the possibility of environmental contamination. A further problem is the unreliability of the data on *P cepacia* or *P maltophilia* colonisation before the routine use of selective media for all specimens, which formerly depended upon the skill and experience of the technician who was looking at culture plates. Also the selective media were introduced at different times for *P cepacia* and *P maltophilia*. In addition, although specimens of sputum were sought at intervals of two weeks, there was inevitably some variation in the parents' adherence to this request.

A further difficulty is our poor understanding of the pathogenicity of micro-organisms that can be recovered in the sputum of patients with cystic fibrosis. The fact that bacteria such as *P aeruginosa* can be recovered from the sputum of patients with cystic fibrosis is no more proof of pathogenicity than the recovery of, for example, *Branhamella catarrhalis*, the presence of which is usually not reported on the assumption that in this disease it is a normal commensal organism. Although the first recovery of *P aeruginosa*, or a change from smooth or rough to mucoid colony types, may coincide with respiratory deterioration, it is difficult to find objective evidence of a causal relationship. It is far from clear whether *P cepacia*, if present in the sputum of a patient with cystic fibrosis, is always or only occasionally a pathogen.[5] Similarly, we have no objective data to support our assumpton that *P maltophilia* is not a pathogen in cystic fibrosis.

Despite these limitations, some conclusions can be drawn from our data. It is clear that the prevalences of *P cepacia* and *P maltophilia* are increasing in the samples we have received, although it is impossible to determine to what extent this increase is due to the introduction of the routine use of selective media. The lack of spread of *P cepacia* to siblings, and the frequent absence of inpatient contact with an affected patient before first recovery of the organism, suggest that cross infection is not the sole route whereby patients with cystic fibrosis become infected, but the possibility of cross infection cannot be excluded from our data. Furthermore, others have found that having a sibling with cystic fibrosis and *P cepacia* colonisation is a significant risk factor for the development of *P cepacia*.[6 7] Inhaled colistin is a possible risk factor for *P cepacia* colonisation because most if not all strains of *P cepacia* are resistant to this agent. The possibility that the use of this agent may encourage the acquisition of *P cepacia* cannot be discounted, although in the present study the greater use of inhaled colistin before the acquisition of *P cepacia* compared with *P maltophilia* was not statistically significant. The published data on the importance of previous antibiotic use are conflicting. In one study, the data suggested a protective effect of aerosolised aminoglycosides,[8] whereas in another study previous use of aminoglycosides (route unstated) was a risk factor for *P cepacia* colonisation.[6] In a third study the previous use of inhaled colistin appeared to have no effect on the risk of *P cepacia* colonisation.[9]

Apart from data on hospitalisation, it was not possible to examine other potential sources of cross infection. Nevertheless, it is of interest that two of the 13 patients who acquired *P cepacia* were first found to have the organism after successfully initiating home intravenous treatment regimens and reducing contact with the hospital ward. Similarly three of the *P maltophilia* group were first found to have the organism at least six months after changing from hospital to home for intravenous antibiotic treatment.

Although our data are not supported by objective sequential measurements of disease severity, such as Shwachman scores, radiological scores or lung function test results, the results suggest that the recovery of *P cepacia* from the sputum is not necessarily associated with a rapid downhill course, although it is undeniable that its presence in a severely affected patient may make antibiotic treatment more complicated and less effective. Other groups have reported either a downhill course[1] or that an increasing proportion of patients with cystic fibrosis who die are colonised by *P cepacia*,[5 7 10] but it is unclear whether there is a causal relationship between colonisation and a worse outcome. In our study, those with *P cepacia* had a poorer outcome compared with the control group with *P maltophilia*, but in only two of the 13 cases did we observe an unexpected deterioration, an infant who died at 5 months of age and a boy of 11 years who has had recurrent acute exacerbations of his respiratory problems ever since the first isolation of *P cepacia*. The majority of our patients, therefore, fit into a category of chronic apparently asymptomatic carriage of *P cepacia*, and indeed, in some patients where it was clinically possible to suspend antipseudomonas treatment for a length of time after first isolating cepacia, we have failed to reculture the organism for up to 18 months.

There is an urgent need for further studies of the possible cross infection of many potential pathogens in cystic fibrosis, including *P cepacia* and multiple drug resistant strains of *P aeruginosa* or *Staphylococcus aureus*. It is regrettable that doctors and patients are currently being obliged to make decisions about segregation and cohorting of patients in the absence of adequate objective published scientific data on the risks or mode of cross infection.

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Prospective evaluation of the Paediatric Risk of Mortality (PRISM) score

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Abstract

The performance of the admission day Paediatric Risk of Mortality (PRISM) score for outcome prediction was assessed prospectively in 270 consecutive admissions, aged 3 days to 18·6 years, to a paediatric intensive care unit. Using a cut off of $r=0{\cdot}00$ (expected mortality=50%), the overall sensitivity (correct prediction of death) was 48% while specificity (correct prediction of survival) was 99%, comparable with the original validation data of the score in the USA. Outcome prediction was most accurate when the stay in the paediatric intensive care unit was between one and four days. Sensitivity was appreciably lower for operative patients (17%) compared with non-operative patients (71%) because of a failure to predict deaths after cardiac surgery. The sensitivity (41%) and specificity (99%) using five variables (systolic blood pressure, Glasgow coma scale, carbon dioxide tension, and serum bicarbonate and serum calcium concentrations) was similar to that using all 14 variables. Six variable ranges related differently with non-survival compared with the score.

It is concluded that the performance of the PRISM score is institution independent and good for short stay patients. It underpredicts deaths after cardiac surgery. Only five variables may be needed for satisfactory outcome prediction. Some of the variables need reweighting for paediatric intensive care units in the UK.

Scoring systems in paediatric intensive care units are used to measure illness severity, assess therapeutic requirements and efficacy, and determine prognosis. The Clinical Classification System (CCS)[1] and the Therapeutic Intervention Scoring System (TISS)[2] are indirect measures of illness severity. The CCS is a qualitative assessment of care requirements on admission and the TISS is a quantitative measure of therapeutic requirements. The Physiologic Stability Index (PSI) is a more direct measure of illness severity but is time consuming, requiring the use of 34 variables.[3] The Paediatric Risk of Mortality (PRISM) score was developed from the PSI to reduce the number of variables to 14 without losing its predictive power.[4] Although validated in the USA, there are no published studies assessing its performance in paediatric intensive care units in the UK.

We undertook a study in the paediatric intensive care unit at the Royal Hospital for Sick Children, Glasgow (RHSC) to evaluate the usefulness of the admission day PRISM score in predicting mortality in the whole population in the paediatric intensive care unit and in particular subgroups of patients. The usefulness and the weighting of each of the 14 individual variables included in the PRISM score in relation to their effect on mortality in our paediatric intensive care unit was also determined.

Methods

The paediatric intensive care unit at RHSC has 12 beds and is the regional referral centre for the west of Scotland. It has approximately 600 admissions every year from all paediatric specialties including cardiac surgery. The study was conducted over a six month period and consisted of consecutive cases admitted during this time.

For the purposes of the study only the admission day PRISM score was used where the admission day was defined as a variable time period composed of eight or more hours after admission until the bedside nurse's vital sign sheets were changed (7 am in our unit). If less than eight hours' data was accumulated then that data was combined with the next complete time period. The admission day could therefore vary from eight to 31·9 hours except in those children who died within eight hours of admission. In these only the immediate preterminal data were excluded (MM Pollack, personal communication).

All data were recorded on a standardised sheet by one of the authors (GB) and included demographic variables (such as age and sex), length of stay in the intensive care unit and outcome (that is, survival or death) in the intensive care unit, the operative status of the patient, and the 14 physiological dysfunction variables used in the definition of the PRISM score (table 1).

The PRISM score involves: (a) coding each of the 14 variables into an integer value based on the ranges of 'abnormality' for infants and children as defined by Pollack *et al*[4] and (b) adding up these 14 separate integer values for the coded variables. Then, to estimate the probability of death in the intensive care unit for this patient [p(ICU death)], the PRISM score together with age and operative status are combined in a linear logistic form as follows:

$$p(\text{ICU death})=\exp(r)/[1+\exp(r)]$$

where $r=0{\cdot}207\times\text{PRISM}-0{\cdot}005\times\text{age (in months)}-0{\cdot}433\times\text{operative status}-4{\cdot}782$, with operative status=0 if non-operative, 1 if postoperative.

Table 1 PRISM score[4]

Variable	*Age restrictions and ranges*		*Scores*
Systolic blood pressure (mm Hg)	*Infants*	*Children*	
	130–160	150–200	2
	55–65	65–75	2
	>160	>200	6
	40–54	50–64	6
	<40	<50	7
Diastolic blood pressure (mm Hg)	*All ages*		
	>110		6
Heart rate (beats/min)	*Infants*	*Children*	
	>160	>150	4
	<90	<80	4
Respiratory rate (breaths/min)	*Infants*	*Children*	
	61–90	51–70	1
	>90	>70	5
	Apnoea	Apnoea	5
Arterial oxygen tension:fractional inspired oxygen ratio*	*All ages*		
	200–300		2
	<200		3
Arterial carbon dioxide tension (kPa)†	*All ages*		
	6·80–8·66		1
	>8·66		5
Glasgow coma score‡	*All ages*		
	<8		6
Pupillary reactions	*All ages*		
	Unequal or dilated		4
	Fixed and dilated		10
Prothrombin time:partial thromboplastin time ratio	*All ages*		
	>1·5×control		2
Total bilirubin (μmol/l)	*>1 Month*		
	>60		6
Potassium (mmol/l)	*All ages*		
	3·0–3·5		1
	6·5–7·5		1
	<3·0		5
	>7·5		5
Calcium (mmol/l)	*All ages*		
	1·75–2·00		2
	3·00–3·74		2
	<1·75		6
	>3·74		6
Glucose (mmol/l)	*All ages*		
	2·2–3·3		4
	13·9–22·2		4
	<2·2		8
	>22·2		8
Bicarbonate (mmol/l)§	*All ages*		
	<16		3
	>32		3

*Cannot be assessed in patients with intracardiac shunts or chronic respiratory insufficiency. Requires arterial blood sampling.
†May be assessed with capillary blood gases.
‡Assessed only if there is known or suspected central nervous system dysfunction. Cannot be assessed in patients during iatrogenic sedation, paralysis, anaesthesia, etc. Scores <8 correspond to deep stupor or coma.
§Use measured values.

STATISTICAL METHODS

The specific model and coefficients used in the linear logistic regression involving all 14 coded variables was exactly that used by Pollack *et al.*[4] A forward stepwise linear logistic regression was carried out to investigate which of the 14 coded variables was necessary in predicting mortality outcome for our data. This was done using BMDP program PLR.

In our investigation of the nature of the relationship between each of the raw variables and outcome, a non-parametric logistic regression was adopted with the smoothing parameter chosen by cross validation.[5] The aim of this method is to investigate the form of the relationship between each variable and mortality without imposing the linear logistic regression form assumed by Pollack *et al.* A standard χ^2 test of goodness of fit of the linear logistic regression model was used for table 2. Sensitivity (correct prediction of non-survival) and specificity (correct prediction of survival) were calculated at a cut off of $r=0·00$ (expected mortality=50%). The level of significance was taken as $p<0·05$.

Results

A total of 270 children admitted consecutively over six months were included in the study. Their median age was 19 months (range 3 days to 18·6 years). There were 157 boys and 113 girls. The median duration of stay in the paediatric intensive care unit was 2 days (range 0·1–66 days). The primary physiological systems of dysfunction, classified in the same manner as Pollack *et al* were: cardiovascular in 123 patients, neurological in 30, respiratory in 51, and other systems (miscellaneous) in 66. One hundred and forty six children were admitted postoperatively and 124 were non-operative patients.

Based on the logistic regression coefficients defined by Pollack *et al*, which combine all 14 variables in their coded form, our sample of 270 patients was estimated to expect 30·8 deaths whereas in fact 29 were observed. Inspection of survival rates across the different categories of expected mortality used by Pollack *et al* (table 2) showed reasonable agreement. In the patients estimated to have a probability of death in the intensive care unit of between 5% and 15% there were seven deaths where only 4·3 were expected but this discrepancy is only approximately one standard error.

The sensitivity and specificity in relation to the length of stay in the paediatric intensive care unit is shown in table 3. The maximum sensitivity for outcome prediction was between one and four days after admission.

At the same cut off (that is, $r=0·00$) there was an appreciable difference in sensitivity for mortality prediction in operated and non-operative patients (17% and 71% respectively). The specificities however were comparable (100% for operated and 96% for non-operative). The low sensitivity for postoperative deaths occurred because of failure to predict 10 of the 11 deaths after cardiac surgery. Of these unpredicted deaths, three occurred within one day of admission and seven deaths occurred four or more days after admission to the paediatric intensive care unit (median 21 days; range

Table 2 Observed (O) and expected (E) survivors and non-survivors

Mortality risk categories (%)	*Survivors (n=241) (O/E)*	*Non-survivors (n=29) (O/E)*
0–1	81/80·5	0/0·5
1–5	85/84·3	2/2·7
5–15	45/47·7	7/4·3
15–30	21/19·5	4/5·5
30–50	5/4·7	3/3·3
50–100	4/2·5	13/14·5
χ^2	4·2	
p Value	0·12	

*Table 3 Outcome prediction in relation to length of stay**

Stay in paediatric intensive care unit (days)	*No (%) sensitivity*	*No (%) specificity*
0–1	5/10 (50)	33/34 (97)
1–2	4/4 (100)	73/73 (100)
2–3	4/4 (100)	40/41 (98)
3–4	1/1 (100)	18/18 (100)
4–10	0/3 (0)	50/51 (98)
>10	0/7 (0)	24/24 (100)

*Cut off r=0·00 (expected mortality=50%).

4·1–48 days) that is, outwith the range of maximum sensitivity noted above.

Outcome prediction in relation to the primary physiological system of dysfunction was as follows. For children with cardiovascular dysfunction the sensitivity was 14·3% and specificity 100%. There were 14 deaths, 11 after cardiac surgery and three non-surgical deaths (two caused by cardiac failure and one by septicaemia). In addition to the 10 incorrectly predicted deaths after cardiac surgery, the two deaths caused by cardiac failure were also not predicted. These two patients stayed in the paediatric intensive care unit for four hours and 15 days respectively. In two groups of patients the number of non-survivors was too small to give any clear impression. Among children with respiratory dysfunction only one out of three deaths was correctly predicted and for patients with neurological dysfunction all three deaths were correctly predicted. The specificity in these two groups was 100% and 96·3% respectively. Performance was best in the miscellaneous (other systems) group. Sensitivity was 88·9% (eight out of nine deaths correctly predicted) and specificity 96·5%.

Using the coded forms of the variables, stepwise linear logistic regression on outcome identified only five of the coded variables (out of the 14 used in the score) to be significantly and interdependently associated with mortality. These were: systolic blood pressure, Glasgow coma scale, carbon dioxide tension, and serum bicarbonate and serum calcium concentrations.

The sensitivity and specificity based on these five coded variables in predicting outcome are similar to that using all 14 variables on our data and the original validation data of Pollack *et al*.[4] The sensitivity was slightly reduced, however, because of a difference of two correctly predicted deaths one of whom is exactly on the cut off point of 50% using the 14 variable model of Pollack *et al* (table 4). Moreover most of the nine excluded variables were not significantly associated with outcome at any stage.

Analysis of individual variables based on our data revealed differences in their relationship with probability of non-survival compared with the original data of Pollack *et al*.

(1) Systolic blood pressure—High values of systolic blood pressure were not related to non-survival (contrary to the data of Pollack *et al*). However there was a clear relationship between low systolic blood pressure and non-survival (fig 1).

(2) Diastolic blood pressure—None of the 270 patients had a diastolic blood pressure of greater than 110 mmHg. Unlike Pollack *et al* we found a clear relationship between low diastolic blood pressure and non-survival (fig 2).

(3) Heart rate—Two hundred and thirteen out of 270 (79%) patients scored maximum points for this variable. For all other variables most

*Table 4 Comparison of sensitivity and specificity of five against 14 coded variables**

Variables	*No of patients*	*Sensitivity (%)*	*Specificity (%)*	*Overall correct (%)*
5†	270	41	99	93
14	270	48	99	93·3
Pollack *et al*[4] (original validation data)	1227	51	99	95

*Cut off r=0·00 (expected mortality=50%).

†Systolic blood pressure, Glasgow coma scale, arterial carbon dioxide tension, and serum bicarbonate and serum calcium concentrations.

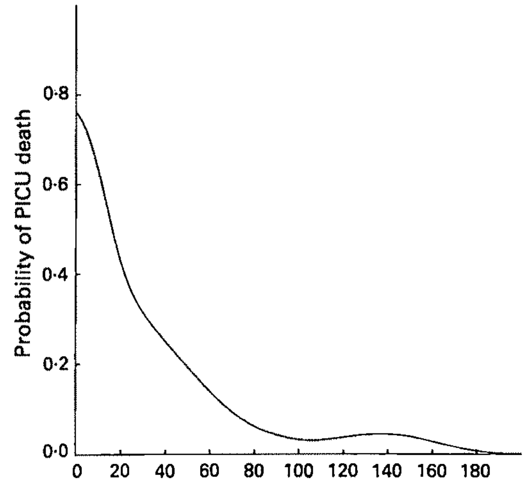

Figure 1 Relationship between probability of death in a paediatric intensive care unit (PICU) and systolic blood pressure.

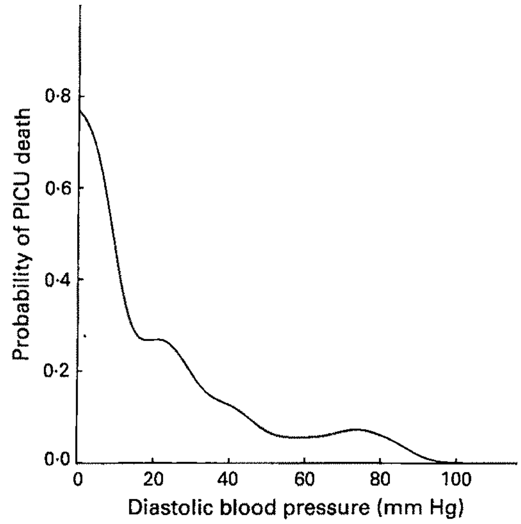

Figure 2 Relationship between probability of death in a paediatric intensive care unit (PICU) and diastolic blood pressure.

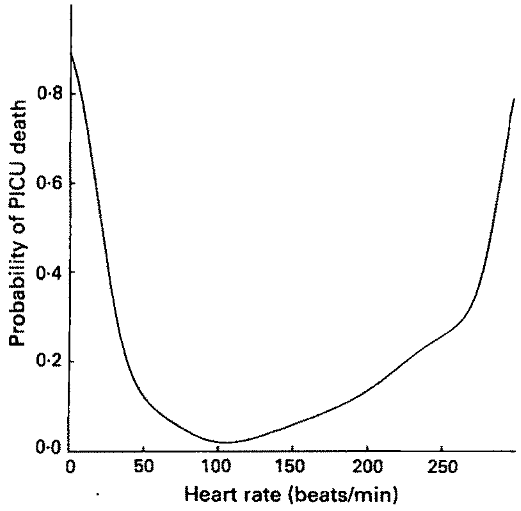

Figure 3 Relationship between probability of death in a paediatric intensive care unit (PICU) and heart rate.

survivors scored 0. A considerable rise in probability of non-survival occurred only above a heart rate of 200/minute and below 50/minute (fig 3).

(4) Prothrombin time:partial thromboplastin time ratio—There was a steady increase in predicted mortality up to a ratio of 2·5 times control; a sharp increase occurred thereafter (fig 4).

(5) Serum bilirubin—Only one patient scored for this variable—that is, had a bilirubin concentration greater than 60 μmol/l.

(6) Serum potassium—Concentrations greater than 7·5 mmol/l were associated with a much greater chance of non-survival than concentrations of potassium less than 3 mmol/l, although both ranges score 5 points each (fig 5).

In general we gain the impression that not only are all 14 variables not necessarily required for prediction of outcome but also that some of the variables that are useful should be scored in a different manner from Pollack *et al* for our patients at least.

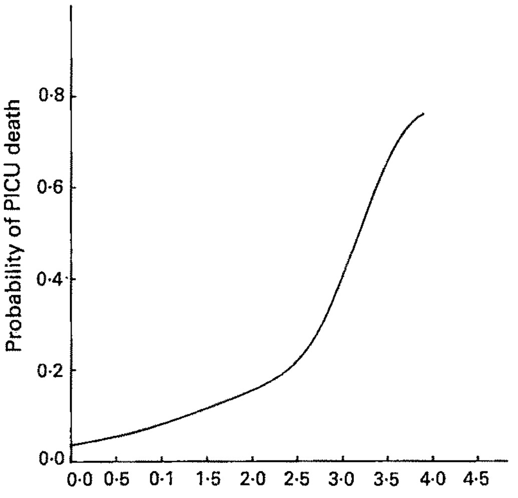

Figure 4 Relationship between probability of death in a paediatric intensive care unit (PICU) and the prothrombin time:partial thromboplastin time (PT:PTT) ratio.

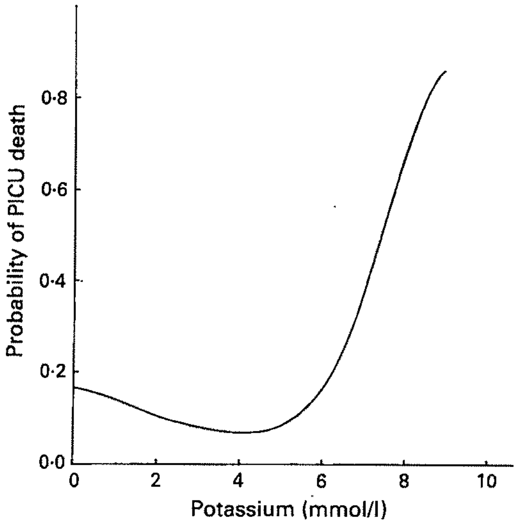

Figure 5 Relationship between probability of death in a paediatric intensive care unit (PICU) and serum potassium concentrations.

Discussion

The overall performance of the PRISM score was good with reasonable agreement between observed and expected mortality across most mortality risk intervals. The observed mortality was greater than expected (by one standard error) in one mortality risk interval (5–15%). However, of the seven deaths in this category five occurred between 12 and 48 days after admission (two of liver failure, two of septicaemia, and one of cardiac failure) and this may have been the main reason why they were not predicted. No avoidable factors could be identified in these deaths. One additional death occurred in a child with relapsed leukaemia and septicaemia in whom full intensive care was withheld on humanitarian grounds because of the hopeless prognosis of the underlying disease. It is possible that this child may have survived admission to the paediatric intensive care unit if full intensive care had been given.

The sensitivity of the score based on the data in our paediatric intensive care unit during the study period was only marginally inferior to the original validation data of Pollack *et al* with comparable specificity and correct classification rates. This confirms that the performance of the score is institution independent. However, it predicts survival better than mortality. The sensitivity of the score could be increased at the expense of specificity by using a threshold other than $r=0{\cdot}00$. Chang has shown that the important issue is to predict death with 100% specificity in contrast to an uncertain outcome; this may result in the earlier withdrawal of treatment than has occurred in the past.[6] In practical terms it is not so important to predict survival as this does not result in any particular action. In adult intensive care where the science of outcome prediction has developed rapidly, dynamic algorithms such as the Riyadh intensive care unit programme based on this concept are currently being evaluated.

The PRISM score was accurate in predicting outcome between one and four days after admission. Only five out of 10 (50%) non-survivors dying within 24 hours of admission were correctly predicted. Two of the unpredicted deaths occurred four and 6·5 hours after admission respectively and insufficient data may have been responsible for underprediction. The remaining three patients had apparently sufficient data but were not correctly predicted. All died after cardiac surgery. The inability of the admission day score to predict death beyond four days suggests that daily PRISM scores are necessary for accurate prediction in longer stay patients as the admission day score does not take into account the dynamics of disease and recovery. A system of dynamic assessment of illness severity such as the Dynamic Risk Index (DRI)[7] needs to be used in addition to daily PRISM scores. One recent study on paediatric trauma patients found daily PRISM scores used in conjunction with the DRI to be accurate in predicting outcome.[8]

The relatively poor prediction of deaths occurring in children whose primary physiological system of dysfunction was cardiovascular and after cardiac surgery may be partly due to either the late occurrence of death (a total of eight cases) or lack of sufficient information (four hours of data) in one case. However, as mentioned above, there were still three deaths which were incorrectly predicted despite apparently sufficient data being available. All three deaths occurred due to cardiac decompensation after cardiac surgery. Previous studies have suggested that this group is relatively poorly predicted by the PSI (on which the PRISM score is based) because in these patients destabilisation is such that multiorgan failure rarely occurs, thereby reducing the 'warning' time.[7] In addition, many patients are transferred to the paediatric intensive care unit sedated and paralysed and cannot be scored for the neurological criteria even if there is suspected dysfunction of the central nervous system. As cardiac surgical patients account for 30–45% of our intensive care unit admissions, this may be a disadvantage. Other studies have shown that the PRISM score does not predict non-survival in children with renal failure,[9] although we could not confirm this due to the small number of patients with this disease.

All 14 variables may not be needed for outcome prediction. A reduction in the number of variables from 14 to five resulted in a loss of sensitivity of only 7% without any loss of specificity. A simplified score using the five variables most closely associated with mortality in our study would be of particular advantage in situations where rapid serial objective assessment of a patient's condition needs to be carried out, for example, during transfer of critically ill children, when they could be scored before, during, and after transfer.

Two variable ranges in particularly, namely high diastolic blood pressure and serum bilirubin, were clearly not useful in predicting mortality. No patient scored for the first and only one patient scored for the second variable range. In addition some of the integer scores for ranges of abnormality in variables may be inappropriate for our patients. For example, low rather than high diastolic blood pressure was clearly related to non-survival in our patients and may need inclusion in the score whereas high values of systolic blood pressure and low values of serum potassium were not significantly related to non-survival. We found a significant rise in predicted mortality beyond a prothrombin time:partial thromboplastin time ratio of 2·5 times control suggesting that an additional score of 4 for values exceeding this level may be appropriate for our patients. Altogether 79% of all patients scored maximally for abnormalities of heart rate suggesting that it was a poor discriminant for non-survival at the ranges suggested in the score. This was partly because many patients were tachycardic because of anaemia, hypotension, or inotropes. The threshold for scoring this variable may need to be upwardly revised in our patients to 170/minute for children and 180/minute for infants.

Despite these differences, we found the PRISM score to be helpful. In addition to prognostication for patient cohorts, it helped us to assess the standard of care that we provided for our patients and it was reassuring to find that this was comparable with that provided in the paediatric intensive care units where the score was initially validated.

Our results are based on a relatively small sample of patients compared with Pollack *et al* but this sample size is equivalent to that of the individual paediatric intensive care units where the score was initially validated. A prospective multicentre study is required to confirm these results.

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Surgical treatment of hyperinsulinaemic hypoglycaemia in infancy and childhood

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Abstract

Despite a greater awareness of hyperinsulinaemic hypoglycaemia, one in three patients has some degree of mental retardation by the time the diagnosis is made. The diagnosis is established by demonstrating high plasma insulin concentrations during an episode of hypoglycaemia. Twenty one hyperinsulinaemic infants and children were referred for surgical treatment after failing to respond to medical management. The surgical procedure of choice is a 95% pancreatectomy. Recurrence of the hypoglycaemia may develop after less radical resections as occurred in one patient who then underwent an extended resection 72 hours postoperatively. Patients who fail to respond to optimal medical treatment should be referred for surgery early and not as a last resort if permanent neurological damage is to be avoided.

Hypoglycaemia may be defined as a blood glucose concentration of less than 2·2 mmol/l. In neonates it is usually transient and responds readily to additional enteral intake of glucose or in more refractory cases to intravenous glucose infusion. Severe intractable hypoglycaemia is rare and more difficult to manage. Delay in recognising the problem and starting treatment exposes the infant to the risk of mental retardation.

In patients with persistent hypoglycaemia it is important to exclude other endocrine disorders; for example hypopituitarism, or inborn errors of metabolism, for example glycogen storage disease. Hyperinsulinism accounts for approximately 1% of all cases with hypoglycaemia,[1] but it is the most common cause of persistent neonatal hypoglycaemia. Laidlaw in 1938, coined the term 'nesidioblastosis' (from Greek 'island') to describe the budding of islet cells from the pancreatic ducts.[2] The specific histological findings in infants with intractable hypoglycaemia were first described by Yakovac *et al* in 1971.[3] The pancreatic tissue shows diffuse β cell and islet cell hyperplasia that is associated with fetal type budding from the pancreatic ducts and disruption of cell ratios and cell to cell contact within the exocrine pancreas.[4]

The diagnosis of hyperinsulinism is made on the following criteria[5]:

(1) Inappropriately raised plasma insulin concentrations for blood glucose values.
(2) Glucose infusion rate >10 mg/kg/minute needed to maintain a blood glucose concentration >2 mmol/l (in the absence of glycosuria).
(3) Low plasma free fatty acids and blood ketone bodies during hypoglycaemia.
(4) A glycaemic response to glucagon despite hypoglycaemia.

The condition is inherited as an autosomal recessive.[6–10] It has been described in association with familial multiple endocrine adenomatosis[11] and been implicated in sudden infant death syndrome.[12–14]

Medical treatment consists of providing sufficient glucose to prevent the hypoglycaemia, which usually requires an intravenous infusion of 15–20% glucose. Diazoxide is still the mainstay of the medical management. It inhibits glucose stimulated insulin secretion and doses of up to 20 mg/kg body weight/day may be necessary. Its action is potentiated by the diuretic chlorothiazide. Somatostatin inhibits insulin release and this hormone or one of its analogues is a useful short term therapeutic adjunct in the preoperative preparation of the infant with refractory hyperinsulinism.[15] Tolerance may develop[16] and surgical treatment is indicated if the patient remains dependent on intravenous glucose.

Patients not responding to optimal medical treatment should be offered surgery at an early stage and not as a last resort. The results of surgery vary according to the extent of the pancreatic resection. The recurrence rate is unacceptably high when the resection is conservative (75–80% pancreatectomy), whereas total pancreatectomy inevitably leads to permanent diabetes and exocrine deficiency. A 95% resection produces the best overall results.[17]

Patients and methods

PATIENTS

In the eight year period, 1982–90, 21 infants and children with severe persistent hypoglycaemia unresponsive to medical treatment were referred for surgical treatment. There were 11 boys and 10 girls whose ages ranged from 8 days to 5 years (fig 1) and birth weights ranged from 2680 to 6800 g. Seventeen (80%) of the infants presented with central nervous system manifestations in the form of twitchings, tremors, limpness, or irritability with or without convulsions within the first three days of life. In three patients who had already had clear evidence of mental retardation presentation was delayed for between 7–24 weeks.

The diagnosis of hyperinsulinism was made according to strict biochemical criteria. Inappropriately high concentrations of plasma insulin were recorded during episodes of hypoglycaemia in all patients (fig 2). Plasma insulin

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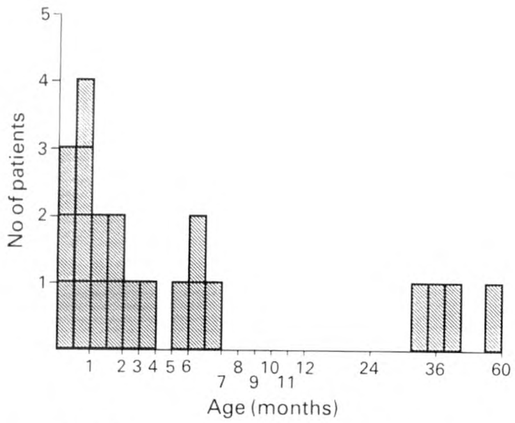

Figure 1 Histogram showing the age of the patients at operation.

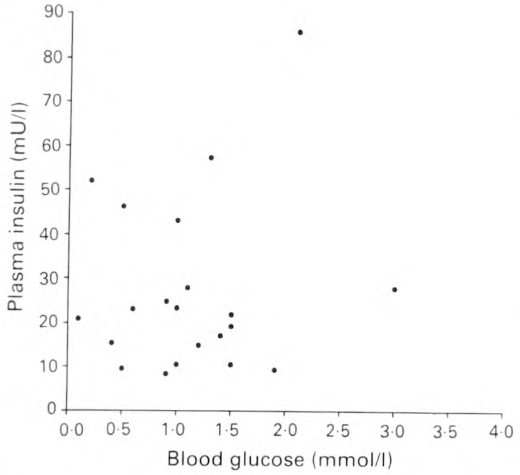

Figure 2 Concentrations of plasma insulin and blood glucose in the patients (to convert mU/l to pmol/l multiply by 7·175).

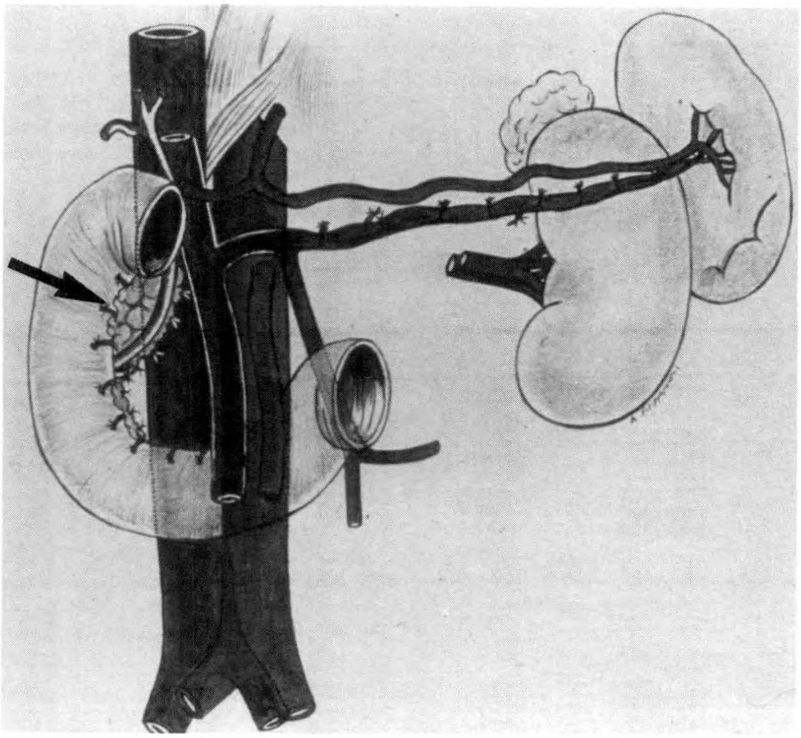

Figure 3 Diagram showing 95% pancreatectomy. The arrow indicates the remnant of pancreas between the common bile duct and the concavity of the duodenum. Note the intact splenic vessels with multiple ligatures of short pancreatic branches.

concentrations ranged from 8·4 to 86 mU/l with a mean of 27·1 mU/l (60·3 to 617·1 pmol/l, mean 194·4 pmol/l).

Diagnostic imaging, including ultrasound scan, computed tomography in most patients, selective coeliac angiography in two, and high resolution magnetic resonance imaging in one patient were singularly unhelpful.

All patients had hepatomegaly, which was considerable in seven infants. Three patients had moderate hypertension and three developed clinical cardiac failure secondary to large volumes of glucose solutions required to achieve normoglycaemia in combination with high doses of diazoxide. Somatostatin was used preoperatively in two patients as a short term measure to control the hypoglycaemia.

Surgery was undertaken as soon as it became evident that the patient could not be maintained on medical treatment alone.

OPERATIVE PROCEDURE

Via a generous upper abdominal transverse muscle-cutting incision, a thorough laparotomy was carried out in search of ectopic pancreatic tissue. The entire pancreas was carefully exposed and examined for the presence of an adenoma, which when present appeared as a reddish-brown nodule on the surface of the greyish pancreas. These lesions were excised and submitted for frozen section histological examination, but because of the coexistence of adenoma and nesidioblastosis particularly in infancy, a full 95% pancreatectomy was carried out. The tail of the pancreas was carefully dissected off the hilum of the spleen and the body of the pancreas mobilised by meticulously exposing and ligating the numerous short pancreatic vessels arising from the splenic vessels. Great care was taken to preserve the splenic vessels to ensure viability of the spleen. Once the dissection had been carried out to the right of the superior mesenteric vessels, attention was turned to the uncinate process which projects posterior to the superior mesenteric vein. Resection of the uncinate process was regarded as an essential step in the operative procedure. After positively defining the course of the common bile duct, the pancreas to the left of the common duct and most of the gland within the concavity of the duodenum was excised. The main pancreatic duct was occasionally identified and ligated. The only pancreatic tissue remaining consisted of that part of the gland between the duodenum and the common bile duct and a sliver of tissue on the medial wall of the second part of the duodenum. This represented approximately 5% of the total volume of pancreatic tissue (fig 3). Bleeding from the raw surface of the gland was meticulously controlled and the wound was closed with a suction drain to the pancreatic bed.

Results

There was no mortality after the 95% pancreatectomy. One patient had a slightly lesser resection due to the presence of pancreatitis and fibrosis. Hypoglycaemia recurred postoperatively and a further resection was carried out on the third postoperative day. Intraoperative injury to the common bile duct was recognised in two infants. In both cases a end to side choledochoduodenostomy was carried out without any immediate or long term effects. Two patients developed adhesion intestinal obstruction within 18 months of surgery, one responding to conservative treatment and the other requiring surgical correction.

Histological examination of the resected pancreas confirmed the diagnosis of nesidioblastosis in all patients. In two an additional pancreatic adenoma was noted in the resected specimen, one of which was recognised at surgery.

Varying degrees of hyperglycaemia occurred in all patients postoperatively. In most infants it developed within 24 hours of surgery and was transient, lasting a few days. Careful monitoring in the immediate postoperative period is, therefore, necessary. Prolonged hyperglycaemia lasting up to 18 months was encountered in four patients and required treatment with insulin. One patient is permanently diabetic; control has been difficult and a total of 4–8 units of insulin daily is required.

Seven patients were referred from abroad and are reportedly doing well on return home. No patient has shown a deterioration of mental function. Exocrine pancreatic function is borderline or low in most cases but only three have evidence of steatorrhoea and two have intolerance to fatty food. Two children require pancreatic exocrine supplementation.

Discussion

The largest review of neonatal hypoglycaemia by Tudor abstracted 122 articles detailing 497 cases published between 1926–1986.[18] Whereas before 1975 the diagnosis of islet cell adenoma was frequent, it has now been superceded by nesidioblastosis. We have reviewed 198 cases published since 1982[10 19–45] and compared them with our 21 cases treated over the same period.

The aetiology and pathogenesis of nesidioblastosis remains unknown. Some authors have described the condition under different names, for example islet cell dysmaturation syndrome,[46] multifocal ductuloinsular proliferation,[47] but the morphological findings are similar with diffuse involvement of the pancreas. Although it is clear that the number of islet cells relative to the rest of the pancreas is highest in the newborn period, it is not known what factors regulate the formation of the β cells in the embryo and postnatally.

There is an important genetic component in neonatal nesidioblastosis as shown by the familial occurrence. Eleven siblings from five families have been reported[6–8 10] and autosomal recessive inheritance is likely. Becker *et al* reported two patients with nesidioblastosis who had a sibling who had died of hypoglycaemia in infancy.[9] Nesidioblastosis has also been documented as a predominant manifestation of multiple endocrine adenomatosis in eight family members over three generations.[11]

With greater awareness of the disease, the diagnosis of nesidioblastosis should be suspected early and confirmed within a few days of birth. Insulin release normally falls as the blood glucose concentration decreases.[48] During severe hypoglycaemia insulin concentrations should be undetectable. Low plasma concentrations of free fatty acids and blood ketones simultaneously support the diagnosis of hyperinsulinism as insulin inhibits lipolysis and hence production of ketone bodies.[49] The absence of ketone bodies as an alternative energy source for cerebral function during hypoglycaemia may explain the high incidence of cerebral damage in these infants. The excess insulin also directs glucose to hepatic glycogen synthesis, probably one factor responsible for the hepatomegaly. The anabolic effect of insulin is also responsible for the high birth weight of some infants.

Though the diagnosis should always be confirmed by measuring plasma insulin, alternative and rapid methods of diagnosis are helpful. The glucose infusion rate, necessary to maintain normoglycaemia, should be calculated. Glucose infusion rates greater than 10 mg/kg/minute in absence of hyperglycaemia or glycosuria are diagnostic of hyperinsulinism (glucose production in the normal newborn is 5–8 mg/kg/minute).[50] All our patients required glucose infusion rates of between 10–25 mg/kg/minute. Diazoxide has been the most widely used drug, inducing hyperglycaemia by mobilising glucagon, stimulating catecholamine secretion, and directly inhibiting insulin release. However, fluid retention is common and three patients developed cardiac failure that responded rapidly to antifailure treatment. Glucagon and prednisolone have been used with varying degrees of success. Somatostatin or a long acting analogue is now the drug of choice and particularly useful in the preoperative preparation of the infant who develops cardiovascular problems from fluid overload and diazoxide treatment. Because somatostatin inhibits not only insulin release but also adrenocorticotrophic hormone and glucagon secretion its use should be combined with glucagon[51] and possibly with cortisol. Tolerance to somatostatin may develop so that surgery is still necessary, although some patients have been given long term treatment.[52]

The time interval between onset of symptoms and operation reported in the literature was 5·55±1·53 months in developmentally normal children compared with 9·65±2·6 months in the mentally retarded infants.[1] In our series the average delay between onset of symptoms and operation was 2·2 months excluding four patients who came to surgery aged between 2·5 and 5 years. Only three patients, two of whom were referred from abroad, had established neurological deficit.

Surgery is indicated when normoglycaemia cannot be reliably maintained despite adequate dosages of glucose, diazoxide, chlorothiazide, and somatostatin. Some patients have been maintained for prolonged periods with medication, notably long term somatostatin[36] but the effect on glucagon and growth hormone release remains a potential risk. They still require regular frequent high carbohydrate-containing feeds but are at risk of developing hypoglycaemia that may result in brain damage, especially during episodes of stress or intercurrent infection. In 1977, Thomas *et al* found that at least 50% of infants undergoing pancreatic resection were mentally retarded at the time of surgery.[1] The incidence of neurological damage was still around 33% in recently reviewed series. It is anticipated that with the increased awareness of the disease and the safety of surgical treatment, neurological sequelae will be prevented in the majority of patients.

Diffuse involvement of the pancreas is more common that localised lesions especially in infancy. Of 188 cases published in the literature from 1982 to 1989, 137 were in infants under one year old, while 61 occurred in older children. In infants, only 7% (10 cases) had localised lesions compared with 40% (24 cases) in the older children. Fifteen infants (11%) had mixed lesions. Limited resection for localised lesions should be reserved for the older age group as diffuse involvement commonly coexists in infants with an apparent localised lesion.

In the majority of patients surgical resection involves a subtotal pancreatectomy. The extent of the resection continues to be controversial. The original subtotal pancreatectomy described by Gross constituted a 65% resection.[53] The resection was carried out to the left of the superior mesenteric vessels and was attended by a 50% recurrence rate.[54] This high recurrence rate spurred surgeons on to carry out more radical resections. Harkin *et al* in 1971 recommended an initial 80–90% resection followed by a total pancreatectomy for surgical failures.[55] McFarland *et al* went even further advocating formal pancreatoduodenectomy.[56] Martin *et al* in 1984, reviewed the results according to the extent of resection in 181 patients.[33] Of 118 patients having subtotal (<80%) resection, 45% required additional treatment and 26% needed reoperation for persistent hypoglycaemia. In comparison, of 63 patients with near total (>80%) pancreatectomy, only 20% needed additional medication and 8% reoperations.[2] In the review of Thomas *et al* of 159 cases, 28% of patients undergoing subtotal pancreatectomy required a second operation compared with 5% of patients with a 95–98% pancreatectomy.[43]

Review of the recent publications indicate that there is still ambiguity in reporting the extent of resection. Resections of less than 80%, that is, to the left of superior mesenteric vessels, are associated with recurrence rate of 26%. A primary 99% resection was performed in six patients (3%) with no recurrence. The majority of the surgeons carried out resections varying between 80 and 95%, with recurrence rates of 24% to 16% respectively (table). Close scrutiny of the operative reports indicates that in many cases the resection was well short of that described above as an adequate 95% resection and this may account for the high recurrence rate. Only one of our patients had an unsatisfactory response to pancreatic resection and required a second resection. In retrospect, it was obvious that this infant did not have a full 95% pancreatic resection at initial surgery.

Extent of resection (literature review 1982–9)

Resection (%)	*No (%) of patients*	*Reoperation (%)*
99	6 (3)	—
90–95	78 (40)	16·6
80–90	68 (34)	23·5
<80	41 (21)	26·8*

*Four of 11 patients required a third resection.

We have no experience with portal blood sampling at operation to determine the adequacy of pancreatic resection as advocated by Carcassone *et al*[24] and Kishi *et al*.[26] Hyperglycaemia or recurrent hypoglycaemia is common in the early postoperative period,[1 30 55] but once normoglycaemia has been established for a few months there is minimal risk of subsequent late complications after surgical resection.

Awareness of the disease entity, early diagnosis, and appropriate treatment are essential if irreversible brain damage is to be prevented. A 95% pancreatectomy has proved highly effective and patients not responding to medical treatment should be referred for surgery *early* and not as a last resort.

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Consultation time, workload, and problems for audit in outpatient clinics

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Abstract

Fifty four of 74 paediatricians in the West Midlands (43 general medical, 11 subspecialist) replied to a postal questionnaire about their outpatient practice: 37 timed each consultation in one clinic. On average, subspecialty consultations lasted 37 minutes for new patients and 29 minutes for review. In general clinics new patient consultations took 23 minutes, review 12. Mean 'single handed' general clinic size was 18, clinics with assistants 24; subspecialist clinics nine and 15. Four to five new patients and nine to 19 review patients were booked per clinic on average; 17/51 clinics used block booking, 34 provided individual appointment times. Mean referral delay was 4·9 weeks, mean clinic wait 22 minutes, and non-attendance averages 16–29%.

Solutions are suggested to four main problems: non-attendance, referral delay, unpunctuality and disorganisation, with audit levels for paediatric outpatient activity.

All paediatricians spend part of their working lives in outpatient clinics. This work is often isolated, unobserved by our peers, and usually not subject to research.[1–3] It is not easy to discover whether an individual workload is excessive and whether other paediatricians have found better solutions to a potentially increasing burden. In particular, time allocated to individual patients seems less and less sufficient, but if more time is provided, then either more clinics must be held, or fewer patients seen.

Methods

I sent all 74 consultant paediatricians who worked in the West Midlands in 1989–90 a questionnaire about their next typical outpatient clinic for newly referred ('new') and follow up ('review') National Health Service patients. They were asked to provide the appointment list, details of their appointment system, and to indicate whether they worked alone or with assisting doctors. I asked them to record the time at the beginning and the end of each consultation.

Table 1 Size and composition of 54 clinics

	General paediatricians (n=43)		*Subspecialist paediatricians (n=11)*	
	Alone (n=16)	*Assisted (n=27)*	*Alone (n=2)*	*Assisted (n=9)*
Mean 'booked' total	18	24	9	15
Range	9–32	15–40	7, 10	9–24
Mean No new patients	4·6	4·8	4·5	
Range	1–8	2–9	1·9	
Mean No review patients	12·6	19·4	9·4	
Range	7–24	10–33	3–18	
% Of new to total patients	26·5	19·8	32·4	
10th–90th centiles (%)	23–38	13–26		

Results

Fifty nine paediatricians replied, and 54 gave data of varying completeness. Eleven provided details of a subspecialty clinic such as developmental paediatrics or cardiology and 43 described general medical paediatric clinics. Eighteen worked single handed in the clinics and 36 had assisting doctors. Forty nine clinics combined new and review patients, two clinics were for review patients only, and three paediatricians saw new and review patients in separate clinics.

COMPOSITION OF CLINICS

Table 1 shows the numbers of new and review patients in 54 clinics. Subspecialty clinics tended to be smaller (mean=12 patients) than general clinics (21 patients), with a larger percentage of new patients (32% compared with 23%). General clinics with assisting doctors were larger than single handed clinics (24:18) and contained a smaller percentage of new patients (20%:27%).

APPOINTMENT SYSTEM

Seventeen paediatricians used 'block booking'—that is, groups of patients with simultaneous appointments, and 34 provided separate appointments for individual patients at the intervals shown in table 2. Eleven paediatricians allocated the same time to new and review patients, while 23 allowed more time for new patients. The systems most frequently used (17 clinics) provided either five or 10 minutes for review patients and 10 or 15 minutes for new patients.

No system provided any flexibility in allocating different amounts of time for different patients, though additional appointments were often inserted between bookings. Twins and siblings were sometimes given a single appointment.

DURATION OF CONSULTATION

Consultation times could be calculated for 37 clinics (table 3). Consultations usually exceeded the time provided: in only six clinics was the timing appropriate. Variations in times within and between clinics was considerable. Consultations lasted longer with new patients, at subspecialty clinics, and with assisting doctors.

Table 2 Appointment system used in 51 clinics

	No of clinics
Block booking	17
Individual timing (min appointments)	34
New patients	
10	10
15	13
20	5
30+	6
Review patients	
5	13
10	11
20	5
30+	5

WAITING TIME

In 33 clinics it was possible to calculate the interval between the booked time and the start of the consultation. These intervals are expressed as means per clinic in table 4, with an analysis of the number of patients having to wait more than 30 and 60 minutes. Longer waiting times were more frequent in clinics with 24 or more patients and when block booking systems were used. In two subspecialty clinics all the patients were seen on time.

REFERRAL INTERVAL

For new patients only, the interval between their attendance and the date of the referring letter was calculated. Table 5 shows the mean referral intervals for 35 clinics and whether some patients were seen within three weeks, or over seven weeks, from referral.

Table 3 Duration of consultations in 37 clinics (min)

	Overall mean	*Range of means*	*10th–90th centiles*
New patients			
Subspecialists	37	25–45	20–40
General paediatricians	23	11–40	15–32
Review patients			
Subspecialists	29	18–45	20–45
General paediatricians	12	5–20	6–17

Table 4 Waiting time in 33 clinics

Mean waiting time (min)		
Range	0–64	
10th–90th centiles	6–40	
Overall mean	22	
Longest actual wait (min)	0–195	
No of patients with 30+ min wait (No of clinics)		
0	8	33
1–2	6	
3–5	14	
6+	5	
No of patients with 60+ min wait (No of clinics)		
0	14	33
1–2	10	
3–5	6	
6+	3	

Table 5 Interval between referral letter and attendance in 35 clinics

Mean interval (weeks)	4·9	
Median	4	
Range	1–15	
10th–90th centile	2–8	
No of patients with intervals 7+ weeks (No of clinics)		
0	19	35
1–2	9	
4+	7	
No of patients with intervals ≤3 weeks (No of clinics)		
0	11	35
1–≥2	24	

NON-ATTENDANCE

Overall, 187 children did not attend out of 921 booked appointments at 47 clinics (20% non-attendance): this excludes cancelled appointments (table 6). Attendance was better at suspecialty clinics and by new patients; a long referral interval may contribute to non-attendance. There was little difference in attendance at general clinics with or without assisting doctors.

DISCONTINUITY

The paediatricians were asked to select the patient reviewed over the longest period, and to list the doctors this patient had seen on the previous 10 visits; 35 replied. In nine clinics this patient had seen the same consultant on each of the last 10 visits, in 22 clinics the same consultant had been seen on at least half of the visits, and in four the same consultant had been seen on less than half. The most extreme example of discontinuity was the patient who had seen six different doctors at the past 10 appointments.

DURATION OF CLINICS

Clinics were usually scheduled from 9 am–12.30 pm or 2 pm–5.30 pm. The data from 37 paediatricians indicated how much of these 3·5 hours was spent on consultation: the median was 3 hours 12 minutes, with a range from 5 hours to 1 hour 45 minutes.

Twenty one clinics started within 15 minutes of the first appointment, 10 within 15–30 minutes, and six were 30 or more minutes late. Consultants sometimes attributed their lateness to inescapable commitments or inclement weather (the survey was in November). Consultations often continued well beyond the allocated 3·5 hours. Morning clinics were more likely to over-run than afternoon ones (14 of 23 morning clinics, three of 14 afternoon clinics).

Paediatricians recorded the consultation time only, not that spent on other activities such as preparation, teaching, supervision, or dictating letters (although one subspecialist spent 25 minutes answering telephone inquiries from his consultant colleagues).

Discussion

There are limitations to this sample of paediatric outpatient clinics, although 73% of paeditricians in the West Midlands participated. Some replied that to complete a questionnaire, and to time each consultation during a busy clinic, were the 'final straws'. Only one clinic from each

Table 6 Non-attendance in 47 clinics for new and review patients

	All clinics		*11 Subspecialty*		*16 General clinics (alone)*		*20 General clinics (assisted)*	
	New	*Review*	*New*	*Review*	*New*	*Review*	*New*	*Review*
Non-attenders	26	161	1	23	7	56	18	82
Total booked	205	716	33	117	74	201	98	398
% Who did not attend	13	22	3	20	9	28	18	21
% Both new and review	20		16		23		20	

For new patients in 30/47 clinics, all attended; in 5/47 clinics, 2+ did not attend. For review patients the lowest % who did not attend was 6% (1/17 booked) and the highest was 70% (7/10 booked); 10–90th centiles 8–40%.

Table 7 Comparative date: non-attendance, clinic size, and composition

	Non-attendance rates (%)		*Mean No of patients/clinic*			*% Of new/total patients seen*		
	New patients	*Review patients*	*Median*	*10th centile*	*90th centile*	*Median*	*10th centile*	*90th centile*
All paediatric clinics in England (1988)*	13	17	12	NA	NA	18	NA	NA
All paediatric clinics in the West Midlands (1988)*	13	20	12	8	17	18	12	26
Inner city general hospital 1985–6†	25	35	NA	NA	NA	23	NA	NA
Current survey	13	22	14	9	28	26	13	38

*Data supplied by West Midland Regional Health Authority 1989.
†Andrews *et al.*[2] NA=not available.

participant was studied, and 45% of them said the selected clinic was not typical—referring to computer errors, over booking, absent staff, and difficult weather conditions. Though these were sometimes quoted as examples of atypicality, sometimes these were seen as being entirely representative. The concept of a 'typical' clinic may be elusive, discontinuity being a characteristic of hospital activity.

My intention was to discover the length of time of each consultation and the size and workload of my colleagues' clinics, without changing their normal clinic activity, and without introducing selection. Table 7 shows that two other surveys in this region support my data.

Four main problems in paediatric outpatient clinic practice were identified (though they are not unique to paediatrics).

PROBLEMS

(1) Non-attendance

One in five of patients failed to attend. New patients were more likely to attend, particularly those visiting subspecialty clinics.[2] Non-attendance seemed to be associated with block booking, long clinic waiting times, referral delay, and large clinics (over 24 patients), but the sample was too small for statistical analysis.

Andrews *et al* concluded that attendance is closely related to the parents' perception of the importance of the problem.[2] Although others have suggested that unnecessary, automatic reviews ('come again in 3 months') particularly by a succession of junior staff, cause non-attendance,[4–6] this survey did not find that non-attendance was more frequent in clinics with junior staff assisting. Nor was there evidence that review patients often saw a succession of different doctors.

(2) Referral delay

New patients waited on average about five weeks from the date of the referring letter before they were seen, with very considerable variation between clinics (1–15 weeks) but very little variation within any particular clinic. Thus, in the clinic with the longest mean delay of 14·6 weeks, the five patients waited 17, 16, 16, 16, and eight weeks; in the clinic with the shortest delay, the intervals were one, one, one, and two weeks.

Some clinics reserved a few vacant booking spaces for urgent new patients, but most followed the policy of allocating the next available appointment to new patients irrespective of urgency. Twenty four of 35 clinics were able to provide at least one new appointment within three weeks of referral.

A mean wait of five weeks for new paediatric referrals is too long. Valman recommends one week for urgent patients and two to three weeks for non-urgent ones, [7] and with these timings most doctors and patients would concur.

(3) Unpunctuality

The mean interval between the appointment time and the start of the consultation was 22 minutes. In five clinics a quarter or more of the patients waited 30 minutes or longer. In three other clinics, a quarter of the patients waited an hour or more. The longest wait was 3 hours 15 minutes.

This 'waiting time' was calculated without knowing when patients actually arrived. Some paediatricians mentioned that patients using public transport arrived in surges, making appointment systems inoperative. But paediatricians themselves were also late: six clinics began at least 30 minutes late.

Another reason for unpunctuality was the mismatch between the times allocated for consultations (a popular choice was 15 minutes for new and five minutes for review patients) and the mean times needed for consultations (25 minutes new, 12 minutes review).

Some waiting is probably inevitable, even if paediatricians were punctual. Patients will need weighing, measuring, undressing, and perhaps investigation or sample collections. Waiting may not be a hardship in clinics that have child centred playgrounds. Nevertheless, waiting is a tense time and children get fractious. Paediatricians will need to take more time with tense parents and irritable children, and may feel the need to compensate them for their wait by giving them extra time: the next patients then wait even longer.

(4) Disorganisation

Ten paediatricians remarked that the clinic was particularly disorganised, and the records from others instanced various muddles.

Computerised appointment systems produce many large sheets of paper that were hard to read. Patients may be listed not in order of attendance but by registration number or alphabetically. 'Double booking' is frequent, and extra patients are squeezed in between appointments. Twins and siblings may be given simultaneous appointments, though in my experience they each need at least the usual allocation of time, if not more.

Some paediatricians seemed to have little control over the appointment system to judge from their written pleas on the lists, 'Stop this crash booking', 'No more patients *at all*, thanks'. They were engulfed by a system in which overlarge clinics, constantly interrupted by distractions and telephone calls, were always overrunning. There was no space allocated at the start of the clinic for reviewing the casenotes, at the middle for a tea break, or at the end for the dictation of letters. Some disasters (such as freezing fog) may not be predictable but some problems, such as junior staff absences on leave, can be anticipated. It may be inappropriate for consultants to hold outpatient clinics on days when they are on emergency call without middle grade staff: some arrived late because of emergency calls. Paediatricians accustomed to disorganisation conveyed a sense of weary fatalism in their comments: 'Clinic atypical: it started on time', "No notes missing—for once", 'No DNAs [did not attend], usually 4 or 5'. They seemed to be engaged in an activity over which they had little control, yet for which they were ultimately responsible.

SOLUTIONS

Not all clinics were disorganised and inefficient: some were punctual, with realistic appointment intervals and overall size, and their patients did not wait many weeks to be seen. Such clinics were not necessarily in areas of affluence, nor at well staffed hospitals. One requirement for success is the realisation that the consultant has overall control and therefore the power to make changes.

Large clinics with a low ratio of new to review patients are particularly associated with appointment delays and long waiting times and therefore the need for each review appointment must be critically appraised. Experienced paediatricians learn that ward follow up appointments are often redundant: for example, after pyloromyotomy or lobar pneumonia. It may be rewarding to meet satisfied customers, and instructive to the untrained to learn how quickly these patients recover, but not at the expense of an overloaded clinic. Delegation to general practitioners is usually possible.[3 5] Written management protocols may enable the paediatrician to delegate the review of less frequently seen paediatric disorders, with an annual hospital review.

The results of investigations can be conveyed to parents by letter or by telephone. Some paediatricians consider face to face contact is needed, but parents may well find that these brief encounters hardly justified the expense and inconvenience of a journey to hospital. Telephone calls and letters will usually be a quicker way of conveying the good news of a normal result, which is anxiously awaited. Smithells describes his practice of using 'telephone appointments' to supplement the regular review of, for example, epileptics.[1] Sending parents a copy of the letter to the general practitioner after a hospital visit will help them to accept diagnosis and management and will make some return visits unnecessary: the results of investigations can sometimes be added in postscript.

Table 8 Proposed audit levels in general paediatric clinics

Maximum total clinic time (min)	210 (consultation: 180, organisation: 30)
Allocated time/patient (min)	No block booking. New: 30, review: 10–15
Maximum No of patients/clinic	Single handed: 13, +1 assistant: 22, +2 assistants :30
Maximum No of patients/assistant	10
New/follow up	At least 25%
Appointment delay	Urgent: 1 week, non-urgent: 3 weeks
Attendance rate	More than 70%
Follow up continuity	Review patients see consultant >50% visits
Outpatient waiting time	Mean: <30 minutes; no patients wait >1 hour
Audit	Quarterly
Consumer survey	Annual (+ outpatient waiting time check)

Non-attendance is wasteful but widespread: many clinics are run on the risky and inefficient assumption that a quarter of the patients will default. It may be worth asking parents (as well as oneself) whether a further visit is necessary. When review appointments are at long intervals a reminder letter beforehand will help: defaulted appointments were reduced thereby from 20% to 8% in one hospital.[8] Morning clinics are preferred by many parents, and attendance is likely to improve given punctual appointments and adequate consultation time. Punctuality will also be helped by individual appointment times: block booking (34% in this survey) in paediatric clinics does not work well. Habitual non-attenders may need a home visit from a health visitor to find whether further appointments would be kept: instead the paediatrician could make a domiciliary visit.

Consultants must take responsibility for the appointment system, designing a schedule of timing appropriate for their needs. They should read referral letters themselves and allocate appointments by the degree of urgency. Some patients may be seen more appropriately as ward attenders and some may not need to be seen at all but only a letter written to the general practitioner and parents—for example, some inquiries about pertussis immunisation. Spaces in the system should be reserved for urgent appointments, preferably at the start or end of the clinic. Some consultants find that separating clinics for new and review patients improves timekeeping and attendance. Punctuality on the consultant's part is of paramount importance (16% clinics started at least 30 minutes late).

This survey revealed that the chaotic conditions of some clinics made outpatient work (always challenging) very unpleasant. My own solution has been to increase my consultation time and reduce the number of patients reviewed. It is important to provide for dictation time, a tea break, and a preliminary opportunity to read casenotes. Appropriate planning is needed for holidays, absence of junior staff, and the presence of medical students. Only very urgent telephone calls should be referred to the clinic.

AUDIT

Finally, regular audit of outpatient activity will help. Some schemes have been published, but these mainly consists of casenote review.[9–11] An annual consumer survey should uncover other unmet needs, but the providers of the service must be prepared to respond positively. Table 8 lists some proposals for outpatient audit, to apply to general medical paediatric practice.

Size of clinics is crucial: 21 of 40 general medical clinics studied were within the proposed limits, which derive from this survey but have been supported by useful data from another source (K L Dodd, Derbyshire Children's Hospital, 1990, personal communication). I hope that these suggestions will provide the starting point for change: not all paediatricians will find these standards will suit their particular style, nor the needs of their patients. Our service would be considerably improved by these suggestions, and we would be able to join Smithells in praise of outpatients clinics: 'an unrivalled opportunity to practise and demonstrate the holistic approach to paediatrics'.

I thank the West Midland paediatricians who helped with yet another tedious survey and Dr M E MacGregor for his improvements to the manuscript.

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Clinical review of idiopathic versus hepatitis B surface antigen related forms of membranous glomerulonephritis

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Abstract

Clinical features and therapeutical approaches in 10 cases of membranous glomerulonephritis (MGN) have been reviewed in an attempt to identify predictive indices of prognosis, and features distinguishing between idiopathic and hepatitis B surface antigen (HBsAg) related forms of glomerulopathy. Five of these children (age range 8–10 years) had HBsAg associated MGN and the other five (age range 12–16) lacking this antigen were defined as idiopathic MGN. The follow up was nine months to 10 years (mean 4·3 years). All had nephrotic syndrome during the course of their disease. There were no distinguishing clinical features nor any difference in the outcome between these two groups. None of the clinical findings including the presence of HBsAg, adversely affected outcome. All patients in the idiopathic group and three of the five in the HBsAg related group received immunosuppressive treatment. Overall complete remission was achieved in four of the five HBsAg associated patients and in three of the idiopathic patients plus partial remission in one of each group. Immunosuppressive treatment caused no complications, and beneficial results of the treatment particularly in the idiopathic MGN group were observed.

Membranous glomerulonephritis (MGN) is an immunologically mediated disease of the kidney.[1 2] The deposition of circulating immune complexes along the epithelial side of the glomerular basement membrane is the hallmark of the disease.[1 2] Antigenic determinants of hepatitis B virus have been frequently implicated in the aetiology of these immune complexes and in the pathogenesis of the disease.[1–5] As MGN is a rare disease in childhood, reports on prognostic factors are rare both for hepatitis B virus infected patients and for idiopathic cases of MGN.[6 7]

We reviewed our experience at Hacettepe Children's Hospital in Turkey in order to analyse whether any of the clinical features including the presence of hepatitis B surface antigen (HBsAg) affected prognosis, and to review our therapeutic approaches to these patients. We have also aimed to define any distinguishing features between the HBsAg related and idiopathic forms of MGN.

Patients and methods

The clinical data of 10 MGN patients, who had been diagnosed by tissue biopsy between the years 1979 to 1990, were reviewed. Five of these patients were found to have HBsAg in their serum and they all lacked antibodies against this antigen. HBsAg tests were negative in the other five patients.

In all patients, whether HBsAg positive or not, lupus erythematosus (LE) cells, antinuclear and anti-DNA antibodies were repeatedly studied. Patients with signs of systemic lupus erythematosus or any other underlying cause have been excluded from this series. Liver function tests were within normal limits in all.

Laboratory evaluation consisted of: urinalysis, 24 hour urine protein quantification or protein to creatinine ratio in spot urine specimens, concentrations of protein, albumin, creatinine, uric acid, and electrolytes in serum, blood urea nitrogen, and liver function tests. Nephrotic syndrome was defined by the criteria of the International Study of Kidney Diseases in Children: this is protein loss of more than 40 mg/m^2/hour, serum albumin concentration less than 25 g/l, and serum protein less than 60 g/l.[8] Urine protein was quantitated by sulfosalicylic acid in 24 hour urine samples. Partial remission was defined as absence of oedema, return of serum albumin concentration to normal values, and persistent asymptomatic proteinuria; this was a mild to moderate degree of proteinuria which was less than 2 g/24 hours.[1 9] Complete remission was defined as total disappearance of proteinuria while maintaining normal serum protein values. Hypertension was defined as blood pressure raised above the 95th centile for age, as previously described.[10] Haematuria was defined as more than five red blood cells per high power field in the urine sediment. Creatinine clearance was calculated as previously described.[9]

Results

There were two girls and eight boys whose age of onset of symptoms ranged between 8 and 16 years with a mean of 11·4 years. Their follow up ranged from nine months to 10 years with a mean of 4·3 years. Percutaneous renal biopsy was performed within six months of the first symptoms of the disease in all except one patient who had complained of oedema in the last two years of follow up.

Two patients presented with hypertension, and three had hypertensive values during the course of their disease (table). Two of these patients were on corticosteroid treatment when they were noted to have high blood pressure.

Two of the patients (numbers 5 and 8) had presented only with heavy proteinuria exceeding 2 g/24 hours without any oedema, and they

Membranous nephropathy in 10 Turkish children

Patient No	*Sex/age (years)*	*Blood pressure*	*Haematuria*	*HBsAg*	*Treatment*	*Outcome*	*Follow up (years)*
1	M/8	Normal	–	+	None	Complete remission at 2·5 years	4·5
2	M/9	High	+	+	None	Complete remission at 10 years	10·0
3	M/10	High	–	+	Steroids	Complete remission in 4 weeks	1·5
4	M/9	Normal	–	+	Steroids	Partial remission in 4 weeks	0·75
5	M/10	Normal	+	+	Steroids	Partial response to treatment in 6 weeks, 8 years later spontaneous complete remission	8·0
6	M/12	High	–	–	Steroid+ cyclophosphamide	Partial remission in 1 year, complete remission in 8 years	9·5
7	F/13	Normal	+	–	Steroid+ cyclophosphamide	No response to treatment at 2 months, complete remission 2 years later	5·0
8	M/16	High	+	–	Steroid+ cyclophosphamide, Ponticelli protocol	Complete remission after 1 year of Ponticelli protocol	4·0
9	F/12	Normal	–	–	Steroid+cyclophosphamide, Ponticelli protocol (6 months), cyclosporin	Resistant nephrotic syndrome (cyclosporin recently started)	1·0
10	M/13	High	+	–	Steroid+cyclophosphamide	Partial response in 2 months	0·8

had normal serum proteins; they subsequently developed nephrotic syndrome. The rest of the patients were nephrotic at presentation. There was a slight decline in renal function in one of the patients which subsequently returned to normal; creatinine clearance was normal in the other patients. Five of the patients had transient haematuria which was occasionally macroscopic.

HBsAg was detected in five of the patients, constituting the first group shown in the table. All of them received levamisole at a dose of 2·5 mg/kg/day for their antigenaemia but no beneficial effect of this drug has been observed. Two of these HBsAg carriers were randomly chosen not to receive any therapy and spontaneous remission was observed 2·5 to 10 years after the onset of their disease. Chronic liver disease was diagnosed by liver biopsy in one of these patients. The other three patients in the HBsAg group received corticosteroids; complete remission was achieved in two, at four weeks and eight years after the onset of the symptoms, respectively. The latter patient initially had a partial response to steroid treatment, then complete remission was noted three years after the cessation of treatment. Partial remission with persistent moderate proteinuria was noted in the last patient of HBsAg associated MGN group (patient number 4).

Idiopathic MGN patients constituted the second group. All of these five patients received steroid and subsequent steroid plus cyclophosphamide treatment. Complete remission was obtained in three (table). One of these children was in partial remission after a course of steroid and cyclophosphamide; he was then put on cyclic treatment with a three day course of bolus methylprednisone, alternating monthly with chlorambucil as described by Ponticelli *et al.*[11] Oral prednisone at a dose of 0·4 mg/kg/day was given in between. He is now in complete remission and off treatment after a year.

In the fourth patient of the idiopathic MGN group, the Ponticelli protocol was also instituted when no response was obtained with steroid plus cyclophosphamide. Unfortunately there has been no improvement in the clinical or laboratory findings and the patient has recently been put on cyclosporin treatment. In the last patient a partial response has been achieved on the second month of steroid plus cyclophosphamide treatment.

Repeat biopises were not performed in any of these patients.

Discussion

The frequency of HBsAg in MGN was prominent in our study. HBsAg was present in 50% of our MGN cases whereas when our 632 patients with idiopathic nephrotic syndrome were screened only three had HBsAg markers (unpublished data). The prevalence of HBsAg in MGN is similar to the 45% reported from France.[1] On the other hand, in a childhood series from Japan all 11 patients had circulating HBsAg.[5] There have not been many reports relating the presence of the antigen to the prognosis of the glomerulopathy. Kleinknecht and Habib have stated that the prognosis in these patients was 'often favorable'.[1] Although our numbers are inadequate for statistical analysis it is obvious that there are no clear differences between the patients with HBsAg and those without. On the other hand, the patients associated with HBsAg had a rather younger age of onset of their disease. Idiopathic membranous glomerulopathy is known to be most common in the second decade of life.[9] As hepatitis B infection tends to occur somewhat earlier in developing countries, it may be suggested that HBsAg has induced the disease at an earlier age than expected by its natural course.

We have also attempted to analyse whether any of the clinical or laboratory features were relevant factors in prognosis and whether any of these helped to distinguish between the HBsAg related and idiopathic forms of MGN. In the 14 paediatric MGN patients reported from Canada, hypertension was observed in 50% and was the only clinical finding that correlated with adverse outcome.[7] In our series 50% of the patients had occasional hypertensive values but it is hard to draw a similar judgment from our study group. Hypertension was not a feature that distinguished between the HBsAg and the idiopathic groups, being present in two and three children respectively.

When the nephrotic syndrome was present on initial presentation, the presence of haematuria and increased blood urea nitrogen did not appear to influence the final outcome adversely. Haematuria was present in 50% of the cases which was somewhat lower than the 80% and 57% percentages reported by others.[1 7] Haematuria was not a distinguishing feature between the groups.

Thus our results indicate that it is not possible to predict the prognosis of MGN from its clinical features as had been previously suggested in the literature. In our series there was no clinical finding that distinguished clearly between the idiopathic and HBsAg related forms of MGN. Our conclusion is consistent with the observations of Kleinknecht and Habib.[1]

Various reports in childhood series of MGN have concluded that steroids and immunosuppressive treatment do not have any clear achievements.[2 7] This is an important issue in the HBsAg related disease because it has been suggested that steroids might induce the replication of hepatitis virus and may accentuate the adverse effects of HBsAg carriers.[12] The fact that two of our patients entered remission without any treatment questions the beneficial effect of steroids in HBsAg related MGN. Thus immunosuppressive treatment should be used with caution in these cases. On the other hand, immunosuppressive treatment has had no adverse effect on the disease and led to a favourable course in most cases.

Ponticelli *et al*[11] have reported encouraging results in resistant MGN cases with a regimen of six months of pulse methylprednisone alternating with chlorambucil. A beneficial response was achieved in only one of our two patients put on this regimen. This protocol should be tested on more cases of idiopathic MGN before any judgments are drawn.

Overall complete remission was achieved in four of five HBsAg related MGN cases and in three of the five idiopathic cases. There was a partial remission in one patient in each group, but these were followed up for only one year. Although we cannot predict the outcome of these two patients, it can be stated that our MGN cases had a favourable course and we suggest that immunosuppressive treatment should be tried, especially in the idiopathic form of MGN.

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Inhaled frusemide against cold air induced bronchoconstriction in asthmatic children

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Abstract

Inhaled frusemide prevents bronchoconstriction in asthmatic adults induced by various triggers. To determine if frusemide provides similar protection in children, whether this is age dependent and equally effective for central and peripheral airways, we performed a double blind, placebo controlled, randomised, crossover study on the effect of inhaled frusemide on lung function changes induced by cold air challenge in 21 asthmatic children. In addition, we measured diuresis before and after inhalation. Bronchodilatation after frusemide was not observed. However, deterioration in lung function after frusemide, compared with placebo, was significantly diminished: forced expiratory volume in one second (FEV_1) was −5·7% *v* −11·5%, peak expiratory flow (PEF) −7·7% *v* −23·3%, maximum expiratory flow at 50% of vital capacity (MEF_{50VC}) −16·0% *v* −35·2%, and at 60% of total lung capacity (MEF_{60TLC}) −32·4% *v* −61·6%, and specific airways conduction −42·0% *v* −57·7%, respectively. This effect was not age dependent. Diuresis was significantly increased from a mean (SEM) of 198 (34) ml/3 hours before inhaled frusemide to 379 (62) ml/3 hours after nebulisation. We conclude that inhaled frusemide prevents cold air induced bronchoconstriction in asthmatic children and that increased diuresis can be expected with a dose as low as 28 mg of frusemide given by nebuliser.

Recently, the loop diuretic frusemide has regained attention due to its prevention of bronchoconstriction in asthmatic adults if inhaled shortly before various asthmogenic triggers. Bianco and coworkers first reported that inhalation of low doses of frusemide almost completely inhibited the airway obstruction after exercise,[1] ultrasonically nebulised water,[2] and various allergens.[3–5] They demonstrated attenuation of the early and late reaction after allergen challenge, but the reactivity to methacholine improved only during the early response.[3 4] However, bronchodilatation was not observed and frusemide failed to protect if given orally or intravenously.[1 5]

These effects of frusemide, resembling the action of sodium cromoglycate, may provide new insights into the basic mechanisms of asthma. Childhood asthma is different from adult asthma in several respects. We therefore questioned whether inhaled frusemide provides a similar protection in children, whether this is age dependent and equally effective for central and peripheral airways. We chose another indirect stimulus that of hyperventilation of cold air. In addition we measured the diuretic effect of inhaled frusemide, to provide objective data.

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Patients and methods

There were 21 patients (19 boys and two girls) with a mean age of 13·3 (range 8–17) years and mild to moderate asthma who were included in the study after significant bronchial reactivity (decrease in forced expiratory volume in one second (FEV_1) >15%) could be demonstrated by cold air challenge. All patients were nonsmokers and had been free of respiratory infections for one month before the study. Written informed consent was obtained from their parents. The protocol was approved by the hospital ethics committee.

The study was performed on two separate days at the same time of the day within a week after the screening challenge test. Oral drugs and inhaled sodium cromoglycate were withheld for 24 hours and other inhalants for at least eight hours before the test. No patient was receiving inhaled or systemic steroids.

Baseline ratios of FEV_1 to vital capacity (FEV_1/VC) had to be above 75% of the predicted value and were not allowed to differ more than 15% between the two study days. The effect of inhaled frusemide was determined by a double blind, placebo controlled, randomised, crossover study.

After measurement of baseline lung function, 28 mg frusemide (Lasix, Hoechst, 10 mg/ml, pH 9·0, 270 mosm/kg) or 2·8 ml placebo (physiological saline with sodium hydroxide to reach pH 9·0, 283 mosm/kg) was delivered to the patients from a jet nebuliser (Pari-Boy, Medanz) without interruption of the flow for a period of nine minutes. This time period was calculated from the mean (SD) nebulised output of 0·32 (0·05) ml/min measured by weighing before and after inhalation on five occasions. Patients used a mouthpiece and noseclip and were asked to breathe normally.

Pulmonary function tests were repeated within five minutes after nebulisation. This was followed immediately by the cold air challenge to show the maximum protective effect of frusemide. A third lung function test was done 5–10 minutes later. We measured airway resistance (Raw), thoracic gas volume (TGV), and several spirometric values using a volume constant body plethysmography (Bodystar FG 90, Fenyves and Gut) and corrected the results for body temperature and pressure.

Table 1 Baseline lung function (mean (SD) % predicted and range)

	Placebo	*Frusemide*	*p Value*
FEV$_1$/VC	89·2 (7·9) (75·0 to 109·0)	87·9 (6·8) (73·0 to 102·0)	0·227
FEV$_1$	85·1 (11·4) (61·0 to 110·0)	86·1 (11·7) (63·0 to 110·0)	0·498
PEF	80·8 (8·7) (64·0 to 100·0)	81·2 (12·4) (65·0 to 105·0)	0·872
MEF$_{50VC}$	67·7 (18·4) (43·0 to 105·0)	65·4 (15·6) (42·0 to 103·0)	0·374
MEF$_{25VC}$	55·0 (16·9) (30·0 to 92·0)	55·2 (16·7) (33·0 to 100·0)	0·928
MEF$_{60TLC}$	57·1 (27·2) (18·0 to 106·0)	57·7 (22·6) (15·0 to 101·0)	0·893
TGV	137·6 (32·7) (83·0 to 196·0)	134·1 (26·2) (92·0 to 187·0)	0·463
Raw	95·0 (40·0) (41·0 to 181·0)	81·0 (38·0) (23·0 to 179·0)	0·038
sGaw	62·6 (13·6) (17·3 to 135·7)	72·8 (32·4) (22·2 to 161·9)	0·062

Table 2 Change in lung function after nebulisation before cold air challenge (mean (SD) % baseline and range)

	Placebo	*Frusemide*	*p Value*
FEV$_1$/VC	−0·5 (3·6) (−8·1 to 4·2)	2·6 (2·9) (−3·4 to 5·2)	0·106
FEV$_1$	3·7 (4·4) (−3·6 to 9·8)	5·6 (2·5) (0·0 to 7·9)	0·335
PEF	6·3 (8·4) (−6·3 to 24·1)	4·6 (5·3) (−2·8 to 10·8)	0·683
MEF$_{50VC}$	3·3 (11·6) (−18·0 to 23·1)	10·0 (13·0) (−7·3 to 31·5)	0·157
MEF$_{25VC}$	3·3 (10·2) (−13·8 to 22·0)	9·9 (15·1) (−11·1 to 34·3)	0·267
MEF$_{60TLC}$	16·5 (22·1) (−12·5 to 51·2)	16·5 (22·2) (0·0 to 68·4)	0·373
TGV	1·9 (5·3) (−6·6 to 10·3)	2·5 (12·2) (−25·7 to 15·1)	0·887
Raw	6·5 (49·3) (−55·9 to 116·4)	9·1 (21·0) (−19·0 to 52·2)	0·893
sGaw	−11·7 (50·0) (−55·2 to 122·5)	−5·4 (20·9) (−39·5 to 24·7)	0·313

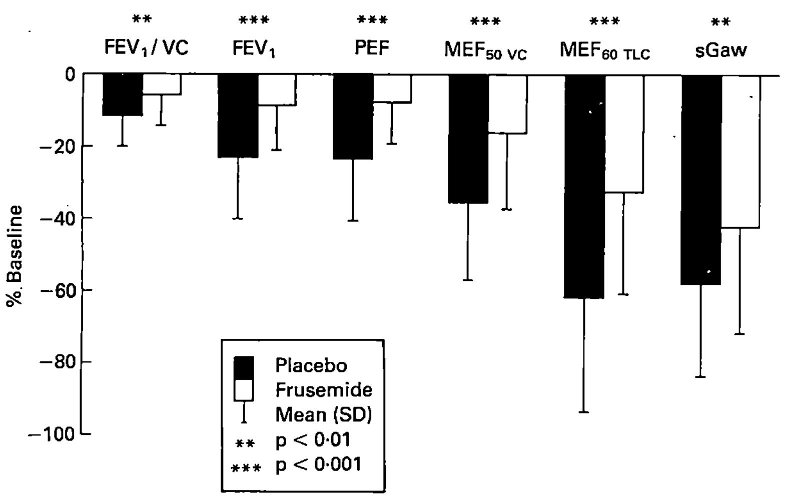

Figure 1 Change in lung function after cold air challenge (expressed as percentage of baseline).

Table 3 Change in lung function after cold air challenge (mean (SD) % baseline and range)

	Placebo	*Frusemide*	*p Value*	*Protection (%)*
FEV$_1$/VC	−11·5 (8·5) (1·2 to −27·2)	−5·7 (7·5) (7·2 to −25·8)	0·006	50
FEV$_1$	−22·9 (17·2) (1·1 to −54·5)	−8·5 (12·3) (12·7 to −42·6)	0·001	63
PEF	−23·3 (17·3) (6·6 to −55·8)	−7·7 (11·4) (14·3 to −32·5)	0·001	67
MEF$_{50VC}$	−35·2 (21·7) (−2·3 to −70·4)	−16·0 (21·2) (33·3 to −60·3)	0·006	55
MEF$_{25VC}$	−33·1 (20·0) (5·7 to −63·3)	−13·3 (24·9) (45·5 to −64·4)	0·008	60
MEF$_{60TLC}$	−61·6 (30·8) (−7·0 to −100·0)	−32·4 (28·2) (44·1 to −93·5)	0·001	47
TGV	39·6 (31·6) (137·1 to −2·7)	20·4 (17·9) (60·2 to −11·9)	0·003	48
Raw	137·0 (159·0) (721 to −6·5)	80·0 (74·0) (255 to −18·0)	0·031	42
sGaw	−57·7 (25·7) (−0·5 to −92·0)	−42·0 (29·6) (28·8 to −82·1)	0·006	27

Cold air challenge was performed after the protocol described by Zach *et al*[6]: the patients hyperventilated (22×FEV$_1$) subfreezing air (−15 to −20°C) with supplementary 5% carbon dioxide for four minutes. We used the Respiratory Heat Exchange System (Jaeger) and monitored the patients by pulse oxymetry (Nellcor, Draeger).

Urinary output as well as the fluid intake were monitored during the three hour period before and after nebulisation. Collection was started after emptying the bladder three hours before inhalation and ended again after voluntary voiding just before the inhalation. Measurement was continued separately until three hours after frusemide/placebo inhalation and ended similarly after voluntary micturition. Fluid intake was recorded during both measurement periods.

Statistical analysis was performed using the paired Student's *t* test. A value of $p<0·05$ was considered significant.

Results

The difference between baseline lung functions on the two study days was not significantly different except for Raw, which was slightly lower on the day receiving frusemide (table 1).

After nebulisation there was a slight increase of spirometric mean values on both study days, but the change in lung function after 28 mg frusemide was not significantly different from that after placebo (table 2).

However, we could demonstrate an evident protective effect of 27%–67% against cold air induced bronchoconstriction after frusemide inhalation in all lung function values after cold air challenge (fig 1, table 3). No statistically significant correlation could be observed between the degree of protection (calculated as the difference in changes of lung function after placebo and frusemide expressed as percentage of the change after placebo) and the degree of baseline lung function impairment (expressed as a percentage of predicted value) or the patient's height, weight, and age. Central airways (reflected by peak expiratory flow (PEF) and Raw measurements), and peripheral airways (shown by TGV and maximum expiratory flow at 25% of vital capacity) were equally protected. Three of 21 patients showed no protection by frusemide in several lung function parameters but due to the small number no subgroup could be identified. On the other hand, in one patient spirometric values improved after nebulisation of frusemide and the following cold air challenge. However, as specific conductance (sGaw) remained constant, an increase in effort rather than bronchodilatation may have occurred.

Urinary output was significantly increased after inhalation of 28 mg frusemide (fig 2, table 4). We found no significant differences in fluid intake between the two groups nor between measurements taken before and after nebulisation (table 4).

Discussion

Our results extend the observations of Bianco and coworkers on exercise, water, and allergen

Table 4 Fluid intake and urinary output during the three hour period before and after nebulisation (mean (SEM) and range)

	Before nebulisation			*After nebulisation*			*Before/after comparison (p value)*	
	Placebo	*Frusemide*	*p Value*	*Placebo*	*Frusemide*	*p Value*	*Placebo*	*Frusemide*
Fluid intake (ml/3 hours)	366·2 (74) (0 to 1200)	296 (47) (0 to 750)	0·303	309·5 (60) (0 to 900)	316·7 (68) (0 to 900)	0·922	0·497	0·725
Urinary output (ml/3 hours)	165·2 (24) (50 to 130)	198·1 (34) (50 to 800)	0·183	180·7 (42) (0 to 900)	378·6 (62) (100 to 1400)	0·001	0·549	0·006

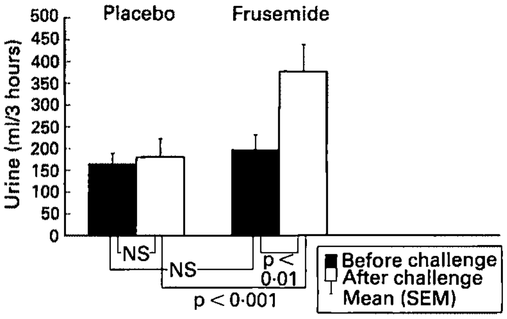

Figure 2 Diuresis during the three hour period before and after nebulisation of placebo or frusemide (expressed as ml/3 hours).

challenge to another indirect acting stimulus—hyperventilation of cold air—and also show that children are protected, as are adults, against bronchoconstriction by low doses of inhaled frusemide. This effect was independent of baseline lung function and was not age related. However, the degree of protection for FEV_1 was 63% in our children compared with 29% recently observed in adults by Grubbe *et al.*[7] Their cold air challenge procedure was only slightly different ($20 \times FEV_1$ for five minutes) which may suggest less response to frusemide in adulthood. However, differences in the severity of asthma or nebuliser output between the two studies may explain the different results.

In addition, we obtained not only FEV_1 but also flow–volume curves, Raw, and TGV. These results show an equal degree of protection after frusemide for central as well as peripheral airways.

As documented in all previous studies, inhaled frusemide did not cause direct bronchodilatation except possibly in one patient. We noticed, however, a slight but similar improvement in many patients after both frusemide and placebo which may be due to the non-physiological pH of the aerosols. Because frusemide is available in either alkaline or acidic solutions, which by themselves may cause non-specific changes in lung function,[8] we stress the importance of equalising the pH of both solutions.

Urinary output was significantly increased after inhaled frusemide. This observation was not mentioned[1 3 5 9 10] or was reported not to be present[4 7 11] in previous studies, except in one case report.[12] Objective measurements, however, had not been obtained. Increased diuresis is unlikely to be responsible for the observed bronchoprotective effect, as this effect was found immediately after frusemide inhalation. Nevertheless, the increase in diuresis within three hours indicates a rapid clearance of inhaled frusemide from the epithelial lining fluid. Therefore doses as low as 28 mg of nebulised frusemide may already cause the well known side effects of long term diuretic therapy. The lowest inhaled dose with a bronchoprotective effect may, however, have a negligible diuretic action and should therefore be evaluated.

Besides a possible role for antiasthmatic treatment, the protective effect of inhaled frusemide on various types of challenge may provide new insights in the pathophysiology of asthma. The protection against cold air challenge corresponds to the prevention of bronchoconstriction after other indirect triggers like exercise,[1] hypo-osmolar stimuli,[2 9] metabisulphite,[11] adenosine-5′ monophosphate,[10] or allergen inhalation.[3 4] By contrast, direct stimuli like metacholine are less effectively counteracted by inhaled frusemide,[3 4 7 10 11] suggesting that frusemide does not directly influence smooth muscle contractility. Similarly, cough induced by low chloride solutions is better protected by frusemide than the capsaicin induced cough.[12] Mast cells, epithelial cells, and neural pathways are more likely targets of frusemide[13] than smooth muscles. The bronchoconstriction response after hyperventilation of cold air is thought to be mainly due to the rise in osmolarity of the epithelial lining fluid. It still remains to be established whether the airway protection by inhaled frusemide is caused by an effect on chloride channels, the sodium–potassium–chloride cotransport, the chloride–bicarbonate exchange,[13 14] the release of prostanoids,[15] or other still unknown factors. The similar action of sodium cromoglycate may help identify the underlying mechanisms.

We conclude that inhaled frusemide is very effective in children in diminishing bronchoconstriction after hyperventilation of cold air. A dose as low as 28 mg does not produce significant bronchodilatation, but causes increased diuresis. Further studies are needed to elucidate the pattern of mediator release after inhaled frusemide to further define the site of action.

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Asthma paralysis (Hopkins' syndrome)

Since Hopkins first described this syndrome in 10 children in Australia[1] in 1974 only 12 more cases have been described including a recent report of two children seen in Toronto (Eli M Shahar and colleagues, *Pediatrics* 1991;**88**:276–9). Children aged between 13 months and 11 years have been affected, there being 14 boys and eight girls. During recovery from an attack of asthma there is a sudden onset of flaccid paralysis of one or more limbs with no sensory loss but often with muscle pain. In 18 children one limb has been affected, in two both legs, and in the remaining two both limbs on one side of the body. Electrophysiological studies point to acute anterior horn cell disease but poliomyelitis is unlikely as all the children have been previously immunised against that disease. An increase in mainly mononuclear cells in the cerebrospinal fluid has been found in less than half (nine of 21) of the children and a few (three of 21) had a raised protein in the cerebrospinal fluid but not such as to suggest Guillain-Barré syndrome. Enteroviruses (not polio) have been isolated in five of 18 cases. The paralysis is permanent with wasting of the affected limbs.

Where does the asthma come in? As usual with the inexplicable, suggestions abound but the truth is we don't know. It's important to be aware of this connection but unfortunately there seems to be nothing you can do to avoid or mitigate the disaster.

ARCHIVIST

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Persistent gastrointestinal symptoms after correction of malrotation

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Abstract

Persistent vomiting, diarrhoea, or intolerance of feeding, are well recognised problems in children after surgical correction of intestinal malrotation. Conversely, intestinal malrotation is a common accompaniment of chronic idiopathic intestinal pseudo-obstruction. We investigated motor activity of the small intestine during fasting in eight children who had persistent vomiting, intolerance of full enteral feeding, or severe diarrhoea after surgical correction of intestinal malrotation. Abnormality of motor function similar to that found in neuropathic pseudo-obstruction was found in seven of the eight patients. Persistence of symptoms after surgical correction of a malrotation is associated with a motility disturbance which seems to be due to a defect of intrinsic enteric innervation. Such a defect may be important in the aetiology of the malrotation.

Malrotation of the midgut results from a disturbance of the process by which the herniated midgut rotates and returns to the enlarging fetal abdominal cavity in the twelfth week of gestation. After birth, small intestinal malrotation frequently presents with acute intestinal obstruction and requires surgical intervention.[1] Symptoms persist after surgery and disordered feeding consistent with abnormal motility is well recognised. As malrotation is common in neuropathic pseudo-obstructive disorders of the midgut, we have studied the motor function of the small intestine in eight children with persistent feeding problems, vomiting, or diarrhoea after surgery in order to investigate whether abnormalities of motility were present which might underlie such problems.

Patients and methods

PATIENTS

Between January 1987 and April 1988, 81 children (aged 1 day to 13 years) with a history of malrotation and intestinal obstruction were seen in the Hospital for Sick Children, London, or the Children's Hospital, Birmingham. Eight (table 1) had persistent severe gastrointestinal symptoms and feeding problems after Ladd's procedure for correction of malrotation, carried out at a median age of 16 months (range 1 month to 13 years). Seven of the eight patients had persistent vomiting. In five of these (patients 1, 3, 6, 7, and 8) vomiting occurred as the enteral intake was increased after surgery, and persisted until the time of referral for investigation. The vomiting was associated with the persistent aspiration of significant amounts of fluid from the stomach, and full enteral feeding could not be established. Three of these five patients were being fed parenterally, one was on continuous gastrostomy feeding, and one was on overnight continuous nasogastric feeding.

In one patient (patient 2), vomiting occurred intermittently and was associated with episodes of abdominal and intestinal distension. One patient (patient 5) had bouts of vomiting associated with severe abdominal pain relieved by cisapride and was intermittently dependent on parenteral nutrition. One patient (patient 4), who had had an ileal resection because of a volvulus, had persistent severe diarrhoea after ingestion of food, not relieved by an exclusion diet, and associated with failure to thrive. One child with vomiting (patient 3) had accompanying pyloric stenosis and a congenitally short small intestine. One patient (patient 8) subsequently developed neurofibromatosis. The patients were referred for investigation at a median time of seven months after surgery (range 0·5 months to five years).

The results of the manometric studies were compared with seven control subjects (aged 2·9–13 years, median 6·9 years), undergoing investigation for suspected gut disease, who were found after investigation not to have a gastrointestinal disease. This group consisted of two patients with chest disease undergoing pancreatic function tests, two patients with short stature undergoing jejunal biopsy, one

Table 1 Clinical features of 8 patients with persistent gastrointestinal symptoms after correction of malrotation

Patient No	*Symptoms*	*Route of feeding*	*Age at operation*	*Age at study*
1	Vomiting on feeding	Parenteral and nasogastric	<1 week	6 weeks
2	Intermittent distension and vomiting	Oral	<1 week	9 months
3	Vomiting on feeding	Via gastrostomy	<1 week	5 months
4	Profuse diarrhoea on feeding, failure to thrive	Oral	<1 week	28 months
5	Vomiting on feeding	Parenteral and oral	8 years	13 years
6	Vomiting on feeding, constipation	Parenteral	22 weeks	7 months
7	Vomiting on feeding	Parenteral	3 weeks	5 weeks
8	Vomiting after bolus feeding	Overnight nasogastric	11 weeks	23 months

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patient with episodic abdominal pain undergoing a pancreatic function test, and two patients with a history of episodes of bowel disturbance due to emotional stress in one case and to transient dissaccharide intolerance in the other case.

MANOMETRY

Motor function of the small intestine after fasting, in particular phase III activity, was used as a probe of the integrity of the enteric nervous system and intestinal smooth muscle. Motor activity was assessed manometrically after a 12 hour fast as previously described.[2] Activity was recorded for a minimum of three cycles of the migrating motor complex where this was present, or for a minimum period of four hours if not present. Mean migrating motor complex duration (cycle length), mean phase III duration, mean phase III pressure wave frequency, a mean phase III motility index for sum of wave amplitudes/duration), and mean propagation velocity of the phase III activity front were measured at the duodenojejunal flexure.

HISTOLOGY

In those patients with severe and persistent symptoms where serious neuromuscular disease was suspected, biopsy specimens of the gastrointestinal tract were taken. Rectal suction biopsy specimens were obtained in four subjects (patients 3, 4, 7, and 8) and examined in our laboratory. Full thickness small intestinal biopsy specimens were obtained from four subjects (patients 1, 2, 3, and 5), and were divided into three for fixation in buffered formalin, glutaraldehyde, and for snap freezing. Morphology was assessed on haematoxylin and eosin stained paraffin and cryostat sections, and the amount of connective tissue was estimated using picrosirius and trichrome stains. Acetylcholinesterase activity was detected in snap frozen tissue. Gluteraldehyde fixed tissue was processed for examination by transmission electron microscopy using standard methods.

Results

MANOMETRY

The indices measured on the manometric recordings are shown in table 2, and representative segments of the recordings from three of the patients are shown in the figure. Patient 1 had no detectable motor activity at the time of the study. Patient 2 had very low amplitude pressure waves as shown by a low motility index, with both failure of propagation and retrograde propagation of some phase III activity fronts. Patients 3 and 4 had a slow frequency of contractions in phase III of the migrating motor complex, suggesting abnormal smooth muscle electrical control activity. In addition, patient 3 showed retrograde propagation of the phase III activity front. Patients 5 and 6 showed failure of propagation of some phase III activity fronts. Patient 7 had abnormally slow propagation of the activity front of phase III activity. Patient 8 had normal fasting activity of the small intestine.

HISTOLOGY

Histological abnormalities in the small intestine were found in three of the four patients in whom full thickness intestinal biopsy specimens were obtained. These abnormalities consisted of distended neuronal axons with ill defined membranes (patient 1), hypoganglionosis of the ileum (patient 2), and vacuolated nerve tracts on electron microscopy (patient 3). Abnormally large nerve trunks in the gastric antrum were found in the fourth of these patients (patient 5). Abnormally large and prominent nerves in the submucosa and myenteric plexus were found in one rectal biopsy (patient 8).

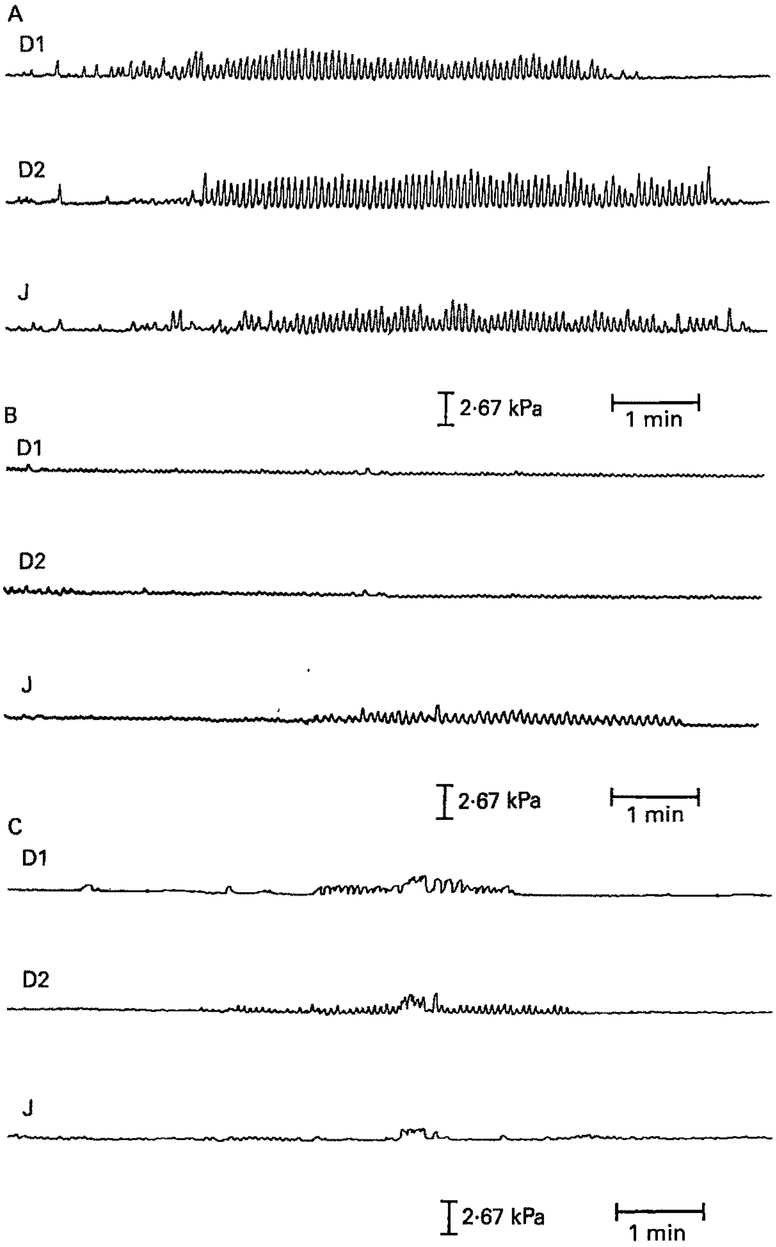
Discussion

The factors which direct the intestine to rotate when the herniated fetal midgut returns to the abdominal cavity at 12 weeks' gestation are not known. By the time the intestine returns into the fetal abdominal cavity, the smooth muscle cells and the neurones which form the enteric nervous system have migrated into place. Although little is known of functional activity of either the enteric nervous system or intestinal smooth muscle cells at this stage of gestation, there is some knowledge of the development of individual neurotransmitters[3] and it is known from animal studies that complex maturational processes influenced by the local microenvironment take place before enteric neurones achieve their final mature form.[4] Malrotation is common in children with pseudo-obstruction, being

Table 2 Indices of motor function of the small intestine obtained from manometric recordings in eight patients with persistent gastrointestinal symptoms after correction of malrotation

Patient No		*Cycle length (min)*	*Phase III duration (min)*	*Phase III frequency (contractions/min)*	*Phase III motility index (kPa/min)*	*Phase III velocity* (cm/min)*	*Non-propagation (fraction)*
1		—	—	—	—	—	0/0
2		30·3	3·1	13·0	6·93	−6·0	2/3
3		32·1	2·4	9·3	39·85	−1·7	0/3
4		43·6	5·0	10·9	11·60	6·6	0/6
5		115·2	7·1	11·0	72·50	3·2	1/13
6		22·7	8·0	11·4	35·50	2·7	6/22
7		35·1	2·5	12·9	22·25	2·0	0/4
8		52·7	3·7	12·8	22·90	19·7	0/5
Normal subjects (n=7)							
Median		79·7	6·2	12·0	24·95	20·7	None
Range:	Lower	35·3	3·2	11·5	10·10	2·2	
	Upper	157·0	7·3	13·0	36·30	48·5	

*Negative numbers denote net orad propagation, positive numbers normal aborad propagation.



Segments of recorded motor activity of the small intestine while fasting showing phase III of the migrating motor complex, from (A) patient 8, showing normal amplitude and frequency of contractions, and normal aborad propagation; (B) patient 4 showing a low frequency of contractions; and (C) patient 2 showing a low amplitude of contractions and failure of propagation of activity to the most distal channel. The ports for channels D1 and D2 are positioned sequentially in the duodenum and the port for channel J is at the duodenojejunal junction; all ports are 5 cm apart.

associated with approximately 12% of all types of pseudo-obstructive disorders in which there is disease of the enteric nervous system either from an early age or expressed congenitally.[5] Thus motor activity may play a part in directing the gut to its correct position within the abdominal cavity. Alternatively, abnormality of the microenvironment in the malrotated intestine may interfere with normal maturation of the neurohumoral control of motor function.

Intestinal motor activity results from the control of inherently contractile smooth muscle cells by the enteric nervous system and polypeptide hormones. The latter are particularly important in the postprandial state whereas fasting activity reflects the activity and integrity of the enteric nervous system. In normal subjects, fasting activity of the small intestine fluctuates in a cyclical manner over a period of approximately 60 to 90 minutes. This cycle is called the migrating motor complex and it consists of three phases, phases I, II, and III. Phase III is a period of rhythmic contractile activity at a frequency of 11–12 cycles per minute (figure). It is followed by a period of quiescence, phase I, and preceeded by irregular contractions, phase II. This motor complex migrates aborally along the small intestine.

The manometric abnormalities present in patients with pseudo-obstruction have been described in both adults[6] and children.[7–9] In the former study, the most common abnormality found was abnormal propagation and/or conformation of the migrating motor complex (found in 25 of the 42 subjects) together with bizarre waveforms. In the latter studies, in children, the fasting abnormalities included in addition absent migrating motor complexes and very low amplitude or absent contractions. In those manometric investigations where full thickness intestinal biopsies have also been done and adequately studied, very low amplitude contractions with poorly differentiated phase III periods have been associated with smooth muscle disease.[8] In contrast, contractile activity of normal or increased amplitude where there is disorganisation, especially loss of cyclic activity, lack of propagation, abnormal propagation or presence of bizarre clusters of contractions, is usually found in patients with neuropathic disorders.[9]

Five of the eight patients in our series had very abnormal motor activity. Four had abnormal propagation and/or conformation of phase III of the migrating motor complex (with or without a low amplitude of contraction), similar to the abnormalities characterised by Stanghellini *et al*[6] and by Wozniak *et al.*[9] One had no motor activity, which was similar to one of the patterns described by Hyman *et al.*[7] Of the other three patients, one had abnormally slow propagation of the phase III complex, and one had an abnormally slow frequency of contraction in phase III, when compared with the values obtained in subjects without gastrointestinal disease. These findings suggest that the majority of our patients who continued to have gastrointestinal problems after correction of malrotation have disturbances of motor function similar to those found in patients with idiopathic intestinal pseudo-obstruction, particularly those with neuropathic disease involving the enteric nervous system.

The histopathology of neuromuscular disease of the intestine has been the subject of a number of reports[10 11] and both muscle and nerve disorders have been described. A recent report of visceral neuropathies, excluding aganglionosis of the colon and Hirschsprung's disease, summarised the most common intestinal conditions.[12] Such conditions included hypoganglionosis, hyperganglionosis or neuronal intestinal dysplasia, glial cell hyperplasia, and absent or diminished argyrophil neurones associated with pyloric stenosis, a short small intestine, and malrotation.[13]

In the present study, one of our patients had hypoganglionosis of the small intestine whose proximal extent was not defined, and had total colonic aganglionosis. Two of our patients had abnormal enteric nervous on electron microscopy. Therefore three of the four patients who had full thickness biopsies had abnormalities in the small intestine previously associated with pseudo-obstruction. The significance of the gastric antral abnormality in the fourth patient (patient 5) is uncertain.

Intestinal neuronal dysplasia can be diagnosed from suction biopsies of the rectum by assessment of acetylcholinesterase-positive nerve cells in the lamina propria, hyperplasia of submucosal neurones and the presence of displaced neurones within the lamina propria.[14] In our series of patients, rectal biopsies were helpful in excluding intestinal neuronal dysplasia and in demonstrating the abnormality in patient 8. It may be that the large nerve trunks seen in this patient, who later developed neurofibromatosis, may indicate early evidence of the spectrum of disorders which include glial cell hyperplasia[12] and intestinal neuronal dysplasia.

One child (patient 4) had a short small intestine due to surgical resection and presented with diarrhoea. There are no published manometric studies of motor function of the small intestine in children with short gut syndrome. Therefore it is not possible to know whether the abnormality found in this case (a slow frequency of contraction in phase III) is secondary to the resection.

Abnormalities of motor function may occur in the period immediately after intestinal surgery. Prolonged ileus is not uncommon in the period immediately after surgery for malrotation. In six of our eight cases the manometric study was performed more than 10 weeks after surgery. The long term effect of surgery on small intestinal activity has not been systematically investigated in children, but in adults who had a proctocolectomy and ileoanal anastomosis, jejunoileal fasting activity was not greatly altered 4–24 months after the operation.[15] We suggest that, in view of the nature of Ladd's procedure and of these adult studies, it is unlikely that the motor abnormalities were caused by surgery in these patients.

Two of the subjects (patients 6 and 7) have now died having failed to take enteral feeding without resultant vomiting, two subjects (patients 1 and 2) are well on parenteral feeding, one (patient 5) is well on enteral feeding and cisapride, and the three remaining subjects suffer intermittent gastrointestinal symptoms on enteral feeding.

Our findings support the notion that in those children where symptoms of gastrointestinal disturbance continue despite surgical correction there is disordered intestinal motor activity. The pattern of disordered activity suggests that it results from either disorder or disease of the enteric nervous system. We therefore postulate that in some children with malrotation aberrant early development of either the enteric nervous system or its microenvironment results both in malrotation of the intestine and its later disordered function.

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Rehabilitation and outcome after severe head injury

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Abstract

After severe head injury, many children continue to experience major cognitive and behavioural problems and consequent educational difficulties, even after good physical recovery. Forty three children referred to the regional multidisciplinary head injury rehabilitation team are described. The clinical outcome at a median interval of 13 months after injury showed that 18 (42%) had persistent neurological impairment and 15 (35%) had an identified need for special educational support. Thirty seven children were further assessed for psychiatric morbidity, cognitive impairment, and classroom performance. Rutter behavioural questionnaires were sent to parents and teachers of head injured index cases and classmate controls matched for age and sex. Index parents scored their children significantly worse in both 'health' and 'habits' and more cases than controls had scores suggesting a psychiatric disorder. Teachers scored index cases significantly worse for five of the traits questioned, but discriminated cases from controls less decisively than parents. Index cases were significantly disadvantaged on teachers' assessments of classroom skills and performance. A need for improved support and training of staff who teach head injured children was identified.

Head injury is a major cause of acquired neurological impairment in childhood. The spectrum of injury is wide and there is frequently a need for prolonged hospitalisation. The scope for recovery is equally wide and may take place over some considerable time.[1] Recovery may be improved by early intervention and good rehabilitation facilities,[2] but in the UK the adequacy of the current service provision for children has been questioned.[3] Few units have reported long term data. Since 1985, in the Royal Liverpool Children's Hospital at Alder Hey, a multidisciplinary team has attempted to optimise recovery and rehabilitation after severe head injury. The work of this team has steadily grown in parallel with an awareness of the problems faced by these children in both the short and medium term. This paper describes the outcome for children so managed from clinical, behavioural and educational standpoints, to provide data against which further service developments may be assessed.

Methods

POPULATION

Between September 1985 and February 1989, children with severe head trauma within the Mersey region and adjoining districts were referred to the neurosurgical unit at Walton Hospital or to one of the Royal Liverpool Children's Hospitals (RLCH) at Myrtle Street or Alder Hey. Neurosurgeons and paediatricians at these sites referred children with post-traumatic neuromotor impairment or delay in recovery for assessment by the head injury team. Children were transferred to RLCH Alder Hey for rehabilitation.

THE HEAD INJURY TEAM

The team was based around the Child Development Centre and comprised representatives from all rehabilitative specialties: medical, physiotherapy, occupational therapy, speech therapy, educational psychology, social work, nursing, and education. All had experience in paediatric rehabilitation and a special interest in head injury. The team was supervised by the senior registrar attached to the regional paediatric neurology unit. Patients were referred directly to the medical team and assessments and therapy organised subsequently as appropriate, as the child recovered. The motor, speech, and educational status of all children were assessed by team members as soon as possible after referral, with the involvement of other specialists as deemed necessary. The team took care to support and inform the families of the injured and to involve them fully in the rehabilitation process. The progress of each child, as hospital inpatient or outpatient, was monitored at team meetings every two weeks attended by representatives from each specialty. Nursing staff from each child's ward, and community based professionals, were also invited to attend as appropriate. Contact was maintained with each child after discharge through the minimum number of visits necessary. An early appreciation of the need for slow reintegration within the mainstream educational system resulted in many children attending the Alder Hey Hospital School on a day patient basis, until there was sufficient recovery to allow return to their mainstream school or completion of statements of need for special educational provision. The importance of medical involvement decreased with time but the senior registrar adopted a facilitative role when no further acute paediatric input was required.

FOLLOW UP DATA

All notes were reviewed in the summer of 1989 and clinical data abstracted for analysis. The parents of each child of school age, for whom six months had elapsed since the injury, were circulated with a Rutter behavioural questionnaire[4] and permission sought to obtain information from the child's school. The head teacher of each school was approached and asked to select, from the index child's class, the child of the same sex with the nearest birthdate to the index child. The parents of these classmate controls were approached in turn and asked to complete a behavioural questionnaire (Rutter A(2)) and for permission to obtain information from the school. Teachers then completed behavioural questionnaires (Rutter B(2)) for both cases and controls, which were supplemented with 10 items from the Conners' hyperactivity scale.[5] Teachers also provided further details concerning the progress of each child, and for the index children completed a questionnaire detailing the information they had received concerning the child and their opinion of the adequacy of facilities available for such children at their school.

Questionnaires were scored as recommended and the alternative assessment of emotional or conduct disorders used. Data were encoded for analysis using the SPSS–PC+ statistical software package. The Mann-Whitney U test and χ^2 statistics were used to compare population and frequency data as appropriate, and the SPSS discriminant and regression options were used for multivariate analysis.

Results

PATIENT DATA

Between September 1985 and March 1989, 43 children were referred for rehabilitation at a median age of 9·4 years (range 2·9–15·0 years). There was an excess of males (32; 74%) and three children were known to have pre-existing disability. Eighteen were admitted directly to RLCH Alder Hey, and three directly to the regional neurosurgical centre at Walton; the remainder were referred from centres without paediatric intensive care facilities. The causes of neurological injury and associated trauma are shown in table 1. Most of the children were pedestrian victims of road traffic accidents. Fourteen children had skull fractures: of these, 11 were vault fractures of which two were depressed, one compound, and one comminuted. There were two facial and one basal fracture. Computed tomography was performed in all children. Fourteen (33%) were normal, while 15 (35%) had intracerebral haemorrhage, 14 (33%) cerebral contusions, and 12 (28%) evidence of cerebral oedema. Fifteen children required surgery and 13 had seizures during the seven days after head injury. Twenty two (51%) received mechanical ventilation for a median time of 60 days (range 2–104 days).

Table 1 Clinical data on 43 patients referred to the head injury team

	No (%) of patients
Source of brain injury	
All road traffic accident	36 (84)
Child as pedestrian	33 (77)
Fall from tree/roof	5 (12)
Other causes	2 (5)
Other significant injuries	26 (60)
Orthopaedic injuries	23 (53)
Surgical procedure(s) required	15 (35)
Tracheostomy	6 (14)
Craniotomy	2 (5)
Debridement/suturing	3 (7)
Fracture reduction	2 (5)
Intracranial pressure monitor	2 (5)
Ventricular shunt	1 (2)
Laparotomy	1 (2)
Embolisation of traumatic arteriovenous fistula	1 (2)
Mechanical ventilation	22 (51)
Seizures (within seven days of injury)	13 (30)

The timing of referral to the head injury team depended upon the child's progress and accessibility, but in most cases contact with team members was made within the first one to two weeks after injury. All children were seen by the physiotherapy, occupational therapy, and educational services. Five also required inpatient speech therapy, and six psychological assessment, usually by the educational psychologist attached to the team. At the time of data collection three remained as inpatients. For the remainder the median admission lasted 60 days (range 5–300 days).

CLINICAL OUTCOME

Clinical problems evident at discharge are shown in table 2, together with the frequency of the same findings at the last reported follow up examination after a median interval of 13 months (range 2–34). Post-traumatic fits were uncommon. No clinical predictors of outcome were observed after univariate or multivariate analysis. However, 13 of the 18 (72%) children with motor impairment at follow up had received mechanical ventilation compared to eight of the 25 (32%) children who were unimpaired (p=0·009). The frequency of overt impairments deceased with time, but a very significant proportion of children had residual impairments of motor function (18; 42%) or behaviour (16; 37%) and 15 (35%) were receiving special educational provision. The high frequency of behavioural and educational sequelae prompted the comparative study which follows.

BEHAVIOURAL OUTCOME

Information on 37 index children and controls was requested from parents and teachers, at a median of 23·7 months after injury (range 6–47 months). Thirty two index and 33 control parents replied (86% and 89%, respectively) and school data were returned for 31 index and 29 control children (84% and 78%).

Table 2 Impairments among 43 head injured children at discharge and at last medical follow up (2–34 months after discharge)

	No (%) at discharge	*No (%) at follow up*
Abnormal neurological signs		
Quadriplegia	2 (5)	2 (5)
Hemiplegia	11 (26)	9 (21)
Diplegia	8 (19)	5 (12)
Dyskinesia	5 (12)	3 (7)
Cranial nerve palsies	2 (5)	0
Seizures	0	1 (2)
Receiving anticonvulsants	8 (19)	4 (9)
Speech disorder	8 (19)	1 (2)
Need for special educational support identified	30 (70)	15 (35)

Table 3 Results of Rutter behavioural questionnaires

	Index children	*Controls*	*p Value*
Median age in months (range)	141 (49–205)	142 (58–198)	
Parents' questionnaire	*n=32* *Median (iqr)*	*n=33* *Median (iqr)*	
Total characteristics scored per child	8·5 (4–15)	4 (2–8)	0·015
Health	3 (2–6·5)	1 (1–2)	0·0002
Habits	3 (2–4)	2 (1–2)	0·0008
No of children with psychiatric disorder	9 (28%)	2 (6%)	0·018*
Teachers' questionnaire	*n=31*	*n=29*	
Total characteristics scored per child	7 (2·5–11·5)	1 (0–7·5)	0·024
Emotional score	2·5 (0–5·5)	1 (0–2)	0·02
Conduct score	2 (0–4)	0 (0–3)	0·12
Hyperactivity rating	3·5 (1–6)	0·5 (0–4)	0·015
Conners' hyperactivity items	8 (2·5–12·5)	2 (0·5–5)	0·003
No of children with psychiatric disorder	11 (35%)	6 (21%)	0·20*

Measures compared using Mann-Whitney U test or χ^2 test (*); iqr, interquartile range.

Index parents scored more behavioural difficulties than control parents (table 3). The median total number of characteristics scored as present per index child was 8·5 (range 0–27) compared with 4 (0–22) for controls (p=0·001). Index parents reported more problems in both 'health' and 'habits' sections of the questionnaire (p=0·032 and p=0·007 respectively). Using the recommended cut off score of 12, nine head injured children (28%) were considered by parental questionnaire to have a psychiatric disorder compared with two (6%) controls (p=0·018). Parents' scores were compared across the range of individual items on the test. Ten characteristics discriminated head injured from control groups: 'attacks of wheezing' (p=0·009), 'temper tantrums' (p=0·001), 'speech impediments' (p=0·005), 'restlessness' (p=0·023), 'squirmy, fidgety' (p=0·05), 'frequently fights or is quarrelsome' (p=0·003), 'often worries' (p=0·005), 'irritable' (p=0·003), 'often disobedient' (p=0·035), and 'bullies other children' (p=0·05). Additionally, there was a trend for head injured children to score more frequently over most of the remaining traits.

A more objective view of each child's behaviour, provided by the teachers' questionnaire, provided less discrimination between the two groups, identifying 11 (35%) index children with behaviour disorder compared with six (21%) controls and similar frequencies of emotional and conduct disorder. Index children none the less had significantly poorer total behavioural scores. Teachers scored head injured children significantly worse than controls on two traits from the Rutter B(2) scale ('squirmy, fidgety child' (p=0·040) and 'often worried, worries frequently' (p=0·050)) and three from the extra Conners' items ('poor attention span' (p=0·025), 'poor co-ordination' (p=0·005), and 'constantly fidgeting' (p=0·050)). The high frequency of problems among controls reflects the classroom matching, many head injured children being in receipt of special educational provision. None the less on most individual items the head injured group showed a trend to score more frequently.

SCHOOL DATA (table 4)

Nine of 32 children (28%) were placed in special schools at the time of follow up by questionnaire, the remainder being in a mainstream school. Four children needed support to remain within their mainstream class and two were in a special needs class within the mainstream school. Educational statements of special needs had been completed for 12 and were planned for five more children, the educational psychologist being actively involved in the management of seven. Sixteen (48%) were coping in the normal classroom without support, although only four children (13%) were not causing their teacher concern. Particular areas of concern varied widely (table 5), and included memory/attentional deficits (n=14), motor skills (n=12), behaviour/personality problems (n=10), language (n=7), and cognition (n=5). Three children were considered to be poor attenders at school.

Table 6 outlines specific learning problems identified by the teacher on direct questioning. Head injured children were significantly disadvantaged compared with controls in most of the areas concerning the processing of information in the classroom, despite the similarities recorded by teachers on the behavioural profile. The disinhibition, inappropriate affect, and disorientation noted frequently during early recovery from head injury appeared to have settled by the time of questioning, although the school routine still posed a problem for many children. Despite the long period of follow up for most of these children the majority had not regained their preinjury skills.

Teachers reported that there were generally enough opportunities to counsel parents of index children but that with nine of the families communication had been poor (table 5). Despite a close liaison between the head injury team,

Table 4 Educational support received by 31 index children

Placement	
Primary	9
With support	1
Secondary	7
With support	3
Special needs	2
Special school	9
Class size	
<10	9
10–20	6
>20	16
Statement of special needs	
Current	12
Planned	5
Educational psychologist involved	7

Table 5 Teachers' subjective view of school performance and parent contact

	Index (n=31)	*Controls (n=29)*
School attendance		
Poor	3	0
Areas of concern		
Any	27	6 (p<0·0001)
Cognitive	5	0
Language/speech	7	0
Motor skills	12	1
Memory/attention	14	1
Behaviour/personality	10	4
Other areas	4	2
Parent contact		
None/infrequent	9	1
Informal/formal	10	12
Counselling opportunities		
None	1	6
As needed	5	9
Planned	6	6

Table 6 Educational questionnaire—teachers' observations

	Index (n=31)		*Controls (n=29)*		*χ^2 test (p value)*
	Applies somewhat	*Applies certainly*	*Applies somewhat*	*Applies certainly*	
Has problems with new tasks	17	8	13	1	0·0075
Has difficulty with speeded tasks	11	16	9	4	0·0007
Has problems retrieving information	13	11	8	0	0·0001
Has difficulty in using appropriate word	13	5	6	0	0·0059
Slow or poorly articulated speech	14	7	5	0	0·0002
Has severe communication problems	9	1	0	0	0·0036
Has impairment of written language skills	10	10	3	1	0·0003
Has difficulties in problem solving	11	12	12	0	0·0005
Appears to be losing academic ground	10	6	3	0	0·0018
Uses excuses to avoid tasks	9	2	7	0	0·060
Tends to get disoriented around school	7	2	2	0	0·073
Tends to get disoriented in classwork	9	1	3	0	0·107
Has problems with school routine	10	1	2	1	0·048
May be disinhibited or show inappropriate behaviour	7	4	4	2	0·443
Thought to have poor self image	9	7	8	1	0·074
Relates well to adults	8	17	6	18	0·849
May be described as					
Careless	9	6	9	1	0·176
Forgetful	10	11	2	1	0·0001
Impulsive	8	2	8	0	0·379
Immature	11	10	9	3	0·060

hospital school and community school, which included personal contact from at least one professional and usually an invitation to attend a team meeting, 27 teachers reported that they would have liked more support with the head injured child, 25 wanting medical and 23 educational support. Within the schools it was also felt that better medical and educational support was necessary when placing a head injured child in mainstream school. This again emphasises the problems experienced by both child and teacher in the reintegration of the head injured child into school.

Discussion

Since the inception of the head injury team, we have become increasingly aware not only of the benefits of early, structured rehabilitation in a multidisciplinary framework, but also of the continuing difficulties and special needs that head injured children have long after discharge from hospital. The poor level of provision for such children has recently been pointed out.[3 6]

Rutter and colleagues, in their detailed studies of psychiatric and cognitive sequelae of head injury in children, found a marked increase in impairment and morbidity among those who had suffered severe head injury as compared with minor head injury or non-cranial trauma.[7–9] We used similar questionnaire techniques, shown to produce reliable and reproducible results, to study patients treated by the head injury team. By using classroom controls, we aimed to identify the extent to which head injury survivors suffer specific educational difficulties. Sequelae of minor head trauma have been described to overreaction by parents and disruption of normal routine.[10 11] In contrast, it is known that major neuromotor impairments are common sequelae of more serious head trauma. Among adults most recovery occurs within six months of the injury[12] but there are few structured data concerning children, although improvements have been observed over a five year period in one study.[1] The generally optimistic view of outcome in the absence of motor impairment has recently been reviewed and challenged.[3 6] We were particularly impressed by the time taken for the return of normal behaviour and educational performance among our children, who had clear disability for many months after physical recovery. It was also clear that relatively few children had returned to their premorbid performance at school.

A major failing of this and many previous studies is the absence of firm preinjury data on which to base the above statements. Reliance is placed on parental reporting, often clouded by the stress and emotional turmoil during the acute period immediately after injury. Children who sustain major head trauma may be placed at risk because of pre-existing neurological, psychological, or social factors. Some studies which have attempted to identify premorbid characteristics of head injured patients have failed to find an excess of previous injury or behavioural problems when compared with controls,[13] although others have found premorbid cognitive abilities[9] and academic performance[14] to be relatively poor. Brown *et al* found an increased incidence of premorbid psychiatric disorder in children with both minor and severe head injuries.[8] There was an unsubstantiated impression that many of our children had pre-existing problems, but there are no control data to support this. Teaching staff, in our experience, are able to provide a more objective assessment of this difficult area. Future prospective data collection should include a formal educational report on each child accepted by the rehabilitation team immediately on referral, together with formal parental data obtained by questionnaire after the acute symptoms have settled.

Another compounding factor which may have enhanced the differences between cases and controls is the effect of prolonged hospitalisation *per se*. This may have produced social, psychological, and educational difficulties in the index children over and above that of the head injury, although Rutter and coworkers found fewer such problems in their control group of children with orthopaedic injuries.[7–9] Future studies should include a further control group of children without head injuries who had similarly lengthy periods in hospital.

Despite these caveats it is clear from these data that major long term behavioural and cognitive sequelae are commonly encountered in children recovering from major head injury, distinct from the more obvious motor problems. Furthermore, no clinical data were able to predict this outcome and in this small series the duration of follow up did not appear to exert a significant effect. Length of coma or ventilation have been used as predictive measures with inconclusive results,[15] a finding supported by the present study.

Computed tomography may be almost routine now in the presence of less severe head injury but relates poorly to outcome and should probably be reserved for those children with signs of focal intracranial lesions.[16] In our patients, findings on computed tomography did not help in the assessment of prognosis for the majority of patients. Seizures, both early and late, were uncommon, and epilepsy is unlikely to have contributed significantly to the educational and behavioural problems.

Head injured children are more likely to have emotional disturbances than control children. The reasons for this observation are complex and the results of the parental behavioural assessments, in particular, must be interpreted with caution.[17] Parents who have been traumatised themselves by observing their child recover from major injury will tend to overreport problems and perhaps even to engender behavioural change in the child by 'overprotection', a feature frequently noted even among parents of children suffering minor injuries.[11] The significant differences among the adverse behavioural traits reported by the index parents, compared with controls, would seem to support this view (table 3) and make the differences observed by the teachers more difficult to interpret.

Of major concern is the high frequency of educational problems and the lack of information with which school personnel are briefed. In the early recovery phase children are disorientated, with a major impairment of short term memory and an inability to persist at a cognitive task for long periods. Although this appears to improve, there remain clear problems in the processing of cognitive information more than six months after the injury. At this stage, children may have no clinical neurological deficit and may be considered to have fully recovered by both doctors and family. None the less, although it has been stated that children continue to improve over long periods after the injury,[1] other studies indicate that around half of a group of head injured children have not made satisfactory progress at school after 10 years.[18] In our experience this continuing improvement is minimal and must not be overstated.

Children who have recovered from major head injury are not lacking in intelligence, but have subtle defects in attentional skills and memory which can be difficult to identify in the busy classroom. The remedial class may not, therefore, be the correct place for such children, unless it is the only area in which an optimal pupil-teacher ratio may be achieved. Wherever they are placed, teachers could be helped by receiving as much information as possible about the children's preinjury abilities, personality and behaviour, and perhaps by using a detailed monitoring system capable of highlighting problems relevant to head injury and showing where progress is being made. Educational policy may need to be reviewed, both to encompass some specific training for teachers about head injury, and also perhaps to change the procedure for issuing statements of special educational needs to allow for the progressive change in needs that is seen during the recovery process. It has been pointed out that head injured children have special needs but are neither sick nor mentally handicapped, and thus at presnt tend to fall in between the areas of responsibility of health and education authorities.[6]

It is thus clear that there is a need for further information on the long term outcome after severe head injury in children. It is also clear that long term support continues to be essential for children who have suffered such injury.

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Post-traumatic tremor in head injured children

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Abstract

In a survey of 289 severely head injured children the prevalence of significant tremor was estimated to be at least 45%. The tremor appeared at any time within the first 18 months after injury and in at least half the cases it subsequently subsided spontaneously. The implications of these findings are to question the mechanism of recovery and suggest that controlled trials of the treatment needed.

Post-traumatic tremor is a recognised complication of head injury in children[1] but little is known about its prevalence and natural history. We had observed a significant upper limb tremor in five of 17 consecutive admissions to a children's head injury rehabilitation unit, between three and 18 months after the injury. In three of the five it subsequently disappeared spontaneously. These observations prompted the present study which was undertaken to determine the prevalence and evolution of post-traumatic tremor.

Method

The study was carried out by a postal survey of subjects chosen from the University of York's Social Policy Research Unit (SPRU) computerised databank of children registered with the Family Fund.[2] About 814 head injured children are known to the fund.

A sample of 289 children stratified by age was selected, so that there were approximately equal numbers of children in each age group, except for the younger age group as there were fewer younger children on the register. The age stratification is shown in table 1.

A questionnaire was devised and was sent by the Family Fund to the parents of each child. To determine the severity of the head injury, questions were asked about loss of consciousness at the time of the injury, the duration of coma, and whether assisted ventilation was required. Movement disorder and disability were assessed with respect to mobility, self help skills and communication, using a modification of a method for recording central motor deficit.[3] Permission was requested for the investigator to examine the fund's file for each child, so that as far as possible the parents' replies could be validated. Ethics committee approval was obtained for the survey.

Table 1 Age stratification of the 289 children

Year of birth	*No of children*
1984–88	31
1979–83	65
1974–78	64
1969–73	65
1964–68	64
Total	289

Results

There were 169 responses obtained in the first three months after distributing the questionnaires. Reminders were sent to all the non-responders. A further 30 questionnaires were subsequently received, giving a total of 199 responses (response rate of 69%). The age distribution of the responders is shown in table 2.

As we had anticipated, some parents confused seizures with tremor and these cases are excluded. There were 131 children who we judged to have had a tremor at some time, in the 199 responders (66%). It was possible to examine files held by the Family Fund in about 60% of these 131 cases and in all of these the presence of tremor as reported by the parents was confirmed in medical notes. Files were examined only if permission had been given by the parents.

In the 30 cases where questionnaires were received after the reminder, none of the children had tremor. Assuming that parents were more likely to respond if their child did have tremor and that tremor may not have been present in any of the remaining 101 non-responders, the prevalence of tremor in the group of 289 cases is 45%.

The severity of the injuries suffered by these children is illustrated in table 3. There was no apparent correlation between severity of the head injury and the time of onset of the tremor. In 131 children who had tremor, the onset was

Table 2 Age at injury of the children in 199 responses

Age (years)	*No of children*
0–5	79
>5–10	66
>10–15	43
Age could not be recalled	11

Table 3 Severity of injuries in 199 responders

Injury or disability	*No (%) of children*
Coma duration >14 days	143 (72)
Required intensive care	192 (96)
Required assisted ventilation	162 (81)
Wheelchair dependent	35 (18)
Totally dependent	28 (14)
Communication difficulties	120 (60)

within two months of the accident in 64 (49%), between two and 12 months in 52 (40%), and in the second year in three (2·3%). No information was available in 12 cases. In 54% of cases the tremor subsided spontaneously over time, it remained unchanged in 31%, and it progressively worsened in 5% for a period of up to three years after the injury.

Discussion

The Family Fund exists to help families of children who are severely disabled, so that it was not surprising to find that most of the subjects in the survey were in this category. However, tremor is probably associated with extensive brain injury. Each of the five patients with tremor in our unit lost consciousness at the time of the accident, remained in coma for a minimum period of three weeks and had residual neurological deficits. None of these patients were on anticonvulsant medications, which could account for tremor as a side effect.

In most children the tremor occurred when a static posture was maintained and was exaggerated by activity and anxiety. It was not observed at rest. The tremor was of large amplitude and low frequency as distinct from the high frequency, low amplitude tremor of anxiety.

Tremor seems to be associated with midbrain lesions. In 1904 Holmes reported on two patients with midbrain glioma at necropsy, who had extremity tremor before their death. Since then there have been further reports of extremity tremor in patients with midbrain lesions. Maki *et al* described four head injured children with basal ganglia infarction visible on the computed tomogram, who developed extremity tremor after their injury.[4] Four of the five children in our unit had evidence of midbrain trauma on computed tomography. (For details of their neuroradiology, see table 4.)

Table 4 Neuroradiological details of four children

Patient No	*Sex/age (years)*	*Results of computed tomography*
1	M/12	Left parietal and right occipital cerebral contusion, small haemorrhages in the corpus callosum and tectum of the midbrain
2	M/13	Compound contusion of the cerebral hemispheres, right thalamic contusion, pontine contusion, intraventricular haemorrhage, and cerebral oedema
3	M/10	Multiple small haemorrhages in the dorsal pons and the tectal plate of the midbrain
4	M/9	Small haematoma of the midbrain, right ventricular haemorrhage, and cerebral oedema

Tremor can be extremely incapacitating and these children may benefit from treatment. Propranolol[5] and dopamine agonists like bromocriptine and stereotactic neurosurgery[6] have been used to treat tremor. However, our observation that tremor subsided spontaneously in three of the patients admitted to our unit and in more than 50% of the cases in the survey is supported by other reports[6]; this has two important implications. Firstly, it raises interesting questions about the mechanisms of recovery and repair in the injured brain and secondly, it suggests that carefully controlled trials of treatment regimens are essential.

It would of course be unwise to draw detailed conclusions from a retrospective questionnaire survey, but our study does confirm that tremor is a common problem in head injured children and contributes significantly to the overall level of disability. There is a need for a prospective study on the incidence and natural history of post-traumatic tremor, and the effectiveness of treatment.

We thank the staff at SPRU, the Family Fund, and the parents who participated; without them this study would not have been possible.

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Energy intake and basal metabolic rate during maintenance chemotherapy

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Abstract

Energy intakes and basal metabolic rates were determined in 26 children receiving chemotherapy in remission from acute lymphoblastic leukaemia or solid tumours and 26 healthy controls matched for age and sex. Body weight and height on the two groups were comparable, although one patient was stunted (height for age) and three others wasted (weight for height). Energy intake in the patients at 7705 kJ/day (1842 kcal) and controls at 7773 kJ/day (1866 kcal)) and basal metabolic rate (BMR) in the patients at 4873 kJ/day (1172 kcal) and controls 4987 kJ/day (1196 kcal) for the two groups were not significantly different. Although the energy intake:BMR ratio for both groups was 1·59, the range of values for the patient group was large (0·96–2·73) and appeared to be greater than that observed in the control group (1·23–2·46). These results demonstrated that during this period of chemotherapy there was no evidence of raised energy expenditure at rest or reduced energy intake in the patient group. No indication of undernutrition in the patients as a group was evident, although some individuals might require further clinical nutritional assessment.

Malnutrition is one of the major problems for children with cancer.[1] Previous studies have shown that at diagnosis these patients are adequately nourished, suggesting that the cause of the malnutrition is predominantly iatrogenic.[2] Though the link between nutritional status and clinical outcome remains incompletely defined, impaired immune function associated with the therapeutic management in combination with malnutrition, either additively or synergistically, may increase the susceptibility of the child to infection.[3] This in turn may influence clinical outcome.

In the long term poor nutrition will also limit growth and development. Growth deficits have been recorded in a large group with a diagnosis of acute lymphoblastic leukaemia but it was unclear whether the deficit was attributable to the disease process itself, infection, or the therapeutic management of the patient.[4]

Attention has been principally directed towards studying the changes in energy intake and expenditure during the initial period of intensive treatment after diagnosis.[5–7] Energy requirements may be raised as a result of cachectic side effects of treatment or infection. The limited number of published studies in children with recently diagnosed cancer have suggested that energy expenditure at rest may indeed be greater than predicted.[5–7] However, in two studies this appeared to be normalised within seven days of initial treatment.[5 6] In the study conducted by Merritt and colleagues basal metabolic rate (BMR) was raised over a period of 30 days.[7] Although all these studies appear to indicate some degree of raised metabolism at diagnosis of cancer and during the first month of treatment, energy requirements during the longer period of maintenance chemotherapy that follows remain unknown.

The purpose of this study was to examine the effect of maintenance chemotherapy alone on the energy intake and BMR of patients without active disease. Measurements of energy intake and BMR were carried out in a group of patients receiving continuous chemotherapy, after the attainment of remission from acute lymphoblastic leukaemia or solid tumours. Their results were compared with those from normal healthy children matched for age and gender.

Subjects and methods

PATIENTS

Twenty six children (aged 5 to 16 years) receiving chemotherapy took part in the study. Sixteen patients with a diagnosis of acute lymphoblastic leukaemia were on Medical Research Council UK acute lymphoblastic leukaemia (UKALL) trials (three girls, 13 boys). Their diagnosis was made a minimum of six months before this study. Measurements of energy intake and BMR were made in the week before their monthly vincristine and prednisolone block.

The remaining 10 patients (seven girls, three boys) included one with chronic granulocytic leukaemia and nine with various solid tumours. They were all on UK Children Cancer Study Group (UKCCSG) trials or related studies. Before participating in this study each patient had received a minimum of three courses of chemotherapy, in addition to initial diagnostic or therapeutic surgery. Energy balance was assessed in the week before a block of chemotherapy. All patients were clinically well and afebrile throughout the study period.

CONTROLS

Local schools were approached for control subjects. Both parents and head teachers gave their consent for the children who volunteered to participate in this study. They were all free from illness at the time the energy balance measurements were made. Ethical approval for the study was granted by the Southampton and South West Hampshire Health Authority.

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METHODS

Weighed dietary intake was recorded for a period of seven days in the standard manner described by Marr, using digital electronic scales (Hanson).[8] The children and their families were instructed in the use of the scales and how to record their food and drink consumption in a notebook provided. The dietary record was checked during a follow up interview with the dietitian (SAB). These were then coded according to the McCance and Widdowson food tables,[9] with additional data from the supplements to the food tables[10–12] and manufacturers' information. Using a computerised database (Microdiet), analysis was carried out to determine the estimated metabolisable energy intake over the seven day period. Energy intakes were expressed in absolute units, corrected for differences in fat free mass, and in relation to that recommended by the Department of Health and Social Security.[13]

In this study, energy expenditure at rest or BMR was defined as the minimum energy expenditure for maintaining essential bodily functions under standardised resting conditions, 12–18 hours' postprandial, in a neutral thermal environment.[14] All measurements were performed between 0730 and 1030 after an overnight fast. BMR was determined by indirect calorimetry using an open circuit ventilated hood system. Oxygen consumption and respiratory exchange ratio were measured to calculate BMR.[15] During the measurement the subjects lay supine on a bed listening to selected music or story tapes. Room temperature was maintained at 22–24°C. The measurements were conducted for a minimum period of 30 minutes after a stable energy expenditure was achieved.

BMR was expressed in kJ/day, corrected for difference in fat free mass, and as a percentage of that predicted on the basis of age, gender, weight, and height.[16]

Height was determined using a Holtain stadiometer. Weight was determined by standing balance scales. Standard deviation (SD) scores were determined for height. Nutritional status was described by determining weight for height as a percentage, and height for age as a percentage, using Tanner and Whitehouse centile charts.[17]

Fat free mass was determined from skinfold thickness (biceps, triceps, subscapular, and suprailiac) measured by Holtain calipers. Both the equations of Brook[18] and Durnin and Rahaman[19] were used to estimate body density because of the wide range of ages within the groups. Siri's equation was used to estimate fat mass.[20] The significance of differences between groups was assessed from the unpaired Student's *t* test.

Results

The characteristics of patients and controls are shown in table 1. The healthy controls had a mean height for age of 101% (range 94–111%) and a mean weight for height of 102% (range 82–132%). Their mean SD score for height was −0·09 with a range of −1·6 to 1·67. Thus all the controls were within +2 SD scores of the median for height. These values would suggest that the control group were representative of the normal healthy population of children.

The mean values for body size and composition of the patients were similar to those of their controls. However, when the range of values for the patients' height for age (52–166%) and weight for height (66–125%) were considered, four patients appeared to be in the poorly nourished range according to the classification of Waterlow *et al.*[21] [22] One patient (with acute lymphoblastic leukaemia) was less than 90% of height for age, or stunted, and three patients (with solid tumours) were less than 80% of weight for height, or wasted. The group with acute lymphoblastic leukaemia tended to be relatively shorter but exhibited a greater weight for their height than the group with solid tumours.

The mean BMR of the two groups whether expressed as kJ/day, or in kJ/kg of fat free mass/day, were very similar (see table 2). When

Table 1 Age and anthropometric variables of healthy controls and patients receiving chemotherapy. Values are mean (SEM)

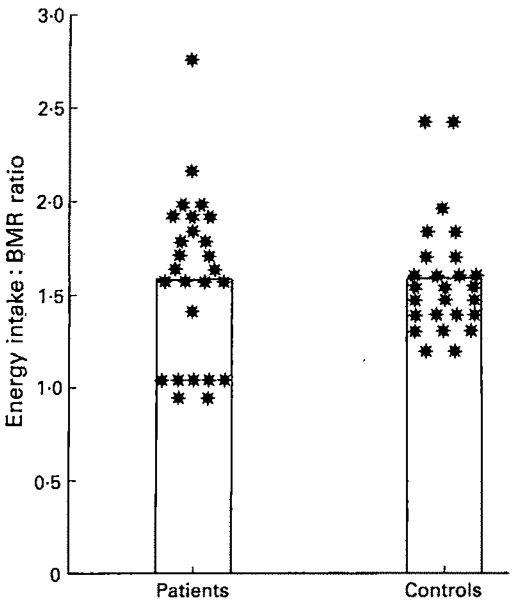
	Controls	*Acute lymphoblastic leukaemia and solid tumour*	*Acute lymphoblastic leukaemia*	*Solid tumour*
Age (years)	10·0 (0·6)	10·1 (0·6)	10·1 (1·0)	10·0 (1·0)
Weight (kg)	33·1 (2·4)	32·4 (2·3)	31·6 (2·4)	33·7 (4·5)
Height (cm)	136·4 (3·4)	138·3 (3·7)	135·5 (4·3)	142·9 (6·7)
SD score	−0·09 (0·16)	0·14 (0·27)	−0·39 (0·33)	0·99 (0·35)
Weight for height (%)	102 (2)	94 (3)	100 (3)*	85 (3)*
Height for age (%)	101 (1)	101 (1)	100 (6)	104 (2)
Fat free mass	27·2 (1·9)	26·3 (1·7)	25·4 (1·9)	27·6 (3·4)

*Solid tumour significantly different from acute lymphoblastic leukaemia at $p<0·01$.

Table 2 Energy intake and BMR of healthy controls and patients receiving chemotherapy. Values are mean (SEM)

	Controls	*Acute lymphoblastic leukaemia and solid tumour*	*Acute lymphoblastic leukaemia*	*Solid tumour*
BMR (kJ/day)	4987 (183)	4873 (207)	4852 (254)	4907 (372)
BMR (kcal/day)	1193 (44)	1166 (50)	1161 (61)	1174 (89)
BMR/kg fat free mass (kJ/kg/day)	197 (9)	194 (7)	198 (7)	189 (13)
% Predicted as % of predicted BMR	101 (3)	98 (2)	97 (2)	100 (3)
Energy intake (kJ/day)	7773 (261)	7705 (459)	7617 (584)	7846 (782)
Energy intake (kcal/day)	1860 (62)	1843 (110)	1822 (140)	1877 (187)
Energy intake/kg fat free mass (kJ/kg/day)	308 (14)	304 (14)	310 (19)	296 (21)
Energy intake as % of RDA[13]	87 (10)	85 (4)	83 (6)	89 (7)

RDA=recommended daily amount.



Individual energy intake: BMR ratio for 26 healthy controls and 26 patients receiving chemotherapy (both acute lymphoblastic leukaemia and solid tumours). Bar indicates mean value for group.

the measured BMR was expressed as a percentage of the BMR predicted for age, gender, height, and weight,[16] there was no significant difference between the two groups. There were no apparent differences in BMR between the two treatment groups.

The range of values for energy intake was larger in the patient group: 4·4–13·2 MJ/day (1053 kcal–3158 kcal) than the control group: 5·5–10·9 MJ/day (1316–2608 kcal). However, the mean energy intake values were very similar whether expressed as kJ/day or kJ/kg of fat free mass/day (see table 2). When the mean energy intake of the two groups were compared as a percentage of the recommended daily amount for energy,[13] the chemotherapy group value (85%) was not significantly different from that of the control group (87%). There were no apparent differences in energy intake between the two treatment groups.

When the energy intake is expressed as a ratio of the BMR the mean values for the two groups were exactly the same, 1·59. The range of values does vary considerably, especially for the patient group: patients, 0·96–2·73 and controls, 1·23–2·46 (see figure). There were no apparent differences in energy intake:BMR ratio between the two treatment groups.

Discussion

Parents of children receiving cytotoxic drugs often express concern that their child may not be eating adequately to satisfy their body's requirements for energy and nutrients. Anorexia and weight loss are prevalent in cancer patients, and those children who have been receiving treatment for long periods of time are more likely to be malnourished.[23] Furthermore several studies which followed up children in long term remission from cancer demonstrated a tendency toward poor growth.[4 24–26] A limitation in growth has to relate to an imbalance between energy intake and energy expenditure and must include consideration of three factors: poor dietary intake, increased faecal losses, and the nature and magnitude of metabolic demand. Deficiencies of specific micronutrients that may also limit growth once energy needs are satisfied should not be overlooked.

Two studies have measured energy expenditure at rest in children with cancer. Kien and Camitta report a limited series of observations in eight children with newly diagnosed acute lymphocytic leukaemia.[5] BMR was measured by indirect calorimetry for a five minute period during which time some of the children slept. The results were expressed as a percentage of published values for normal children and revealed that the mean increase in BMR was 50% (range 16–166%) above normal. This study is frequently cited as evidence of a raised metabolic demand in children with cancer. It should be noted that apart from potential errors associated with such a brief period of measurement, no attempts were made to compare these results with the BMR determined in a control group. It is also not possible to determine whether these measurements were made before or after treatment was initiated.

In a subsequent study by Stallings *et al* greater attention was paid to technical detail and measurements of BMR were made in nine children with newly diagnosed acute lymphoblastic leukaemia before and during the first two weeks of chemotherapy.[6] Energy expenditure at rest was determined in the patients who were subdivided into two groups with differing tumour burden. They found that only the three patients with a high white cell count at diagnosis exhibited a BMR that was 13–45% greater than that predicted from age, sex, and size. The remaining six patients with low tumour burden exhibited BMR values comparable with that predicted from age, sex, and size. The raised BMR of the high tumour burden group rapidly returned to normal with treatment. While chemotherapy treatment *per se* did not appear to raise BMR, changes in substrate utilisation were observed that appeared to be more persistent. They noted that as most chemotherapy programmes for children with acute lymphoblastic leukaemia last up to three years, longitudinal follow up of intermediary metabolism is important to determine whether there is a profound and permanent effect on metabolism, growth, and development.

In this present study energy intakes and BMRs were determined in children receiving ongoing chemotherapy while otherwise well and having no evidence of active disease. Both patients and healthy controls appeared to consume equivalent amounts of energy with their mean values between 13–15% less than their recommended daily amount for energy. Both groups exhibited values for BMR that were comparable, whether expressed in standard units, per kg of fat free mass, or as a percentage of that predicted from age, sex, height, and weight.

The mean ratio of energy intake to BMR (BMR factor) was the same for both groups, 1·59. There is very little published information on energy intake:BMR ratios in children of this age group against which our results may be compared. This value is slightly lower than the desirable energy allowance for populations expressed as a ratio of BMR estimated from patterns of physical activity for this age group (boys 1·76, girls 1·65).[27] The range of BMR factors of the patients was large (0·96–2·73) and appeared to be greater than that reported for the control group (1·23–2·46; see figure).

Seven of the children receiving chemotherapy reported energy intakes that were less than or only slightly greater than their BMR values. These patients were not the ones who fell into the category of being stunted or wasted. Those patients already showing signs of poor growth may have experienced energy deprivation in the past and their metabolism adapted to the reduced intake. There would be no method of measuring whether this was during early childhood, at the time of the initial disease, or during previous treatment.

Though this may be interpreted as evidence that the food intake of these children was insufficient, it is important to recognise that this may also reflect the under-reporting of food intake.[28] Considerable efforts were taken in this study to limit the possibility of inaccurate reporting of food intake. In addition the problem of undereating during the period of measurement should not be ruled out.[29] There was no evidence of energy imbalance, as indicated by measurements of weight, between the start and end of the diary recording. It was not possible to make measurements of habitual physical activity during this study.

This study represents the first occasion in which energy intakes and basal metabolic rates have been determined beyond induction chemotherapy. We found that in the week before chemotherapy the dietary intake of energy and the expenditure of energy at rest of a group of patients receiving chemotherapy gave little evidence to suggest that undernutrition was a problem for these patients. However, the sample size was relatively small, the group fairly heterogeneous and possibly not representative of their respective patient populations. For example the patients with acute lymphoblastic leukaemia were older than a typical patient population. If there is a long term energy deficit leading to poor growth in some children with acute lymphoblastic leukaemia, further studies need to investigate these components of energy balance during other stages of the cycle of treatment and with a younger homogeneous patient group.

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Fever associated with teething

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Abstract

A relationship between teething and fever was sought by examining mothers' reports of the 20 days before the eruption of the first tooth in 46 healthy infants. Twenty infants had a fever of >37·5°C on day 0 compared with seven infants (or fewer) from day 19 to day 4. The danger of attributing fever to teething is emphasised.

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Teething it has been claimed, produces nothing but teeth.[1] Others claim, as did Hippocrates, that 'teething children suffer from itching gums, fever, convulsions, diarrhoea, especially when they cut their eye teeth and when they are very corpulent and costive' (25th aphorism, third book).[2] Illingworth 'searched through the whole of the word literature for evidence of this and found none' (that is, bronchitis, diarrhoea, rash, convulsions, and fever).[1]

This study attempts to address the question of systemic symptoms and signs associated with teething in a scientific manner by a prospective controlled investigation. The research was performed as the result of reading a 'spoof' article that claimed that fever is associated with teething.[3]

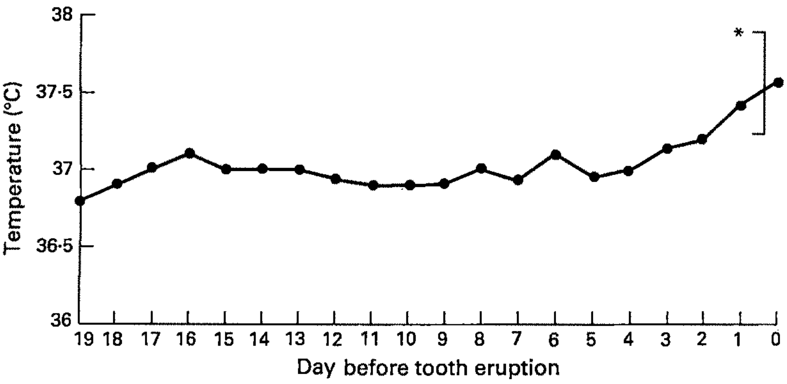

*Figure 1 The mean daily temperature of children by day before eruption of first tooth; *95% confidence interval 37·33 to 37·86.*

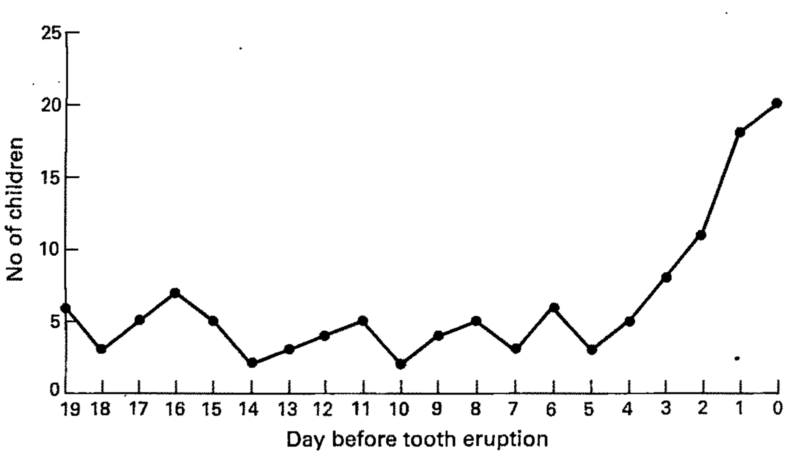

Figure 2 Number of children with fever of >37·5°C by day before eruption of first tooth.

Subjects and methods

Mothers of 46 healthy infants seen between April and September 1988 on a regular basis at the well baby clinic of one of the authors (LJ) were requested to write down the details of a daily examination of their infants on a supplied form. They examined rectal temperature and the gums for evidence of dental eruption and noted if there was any diarrhoea, convulsions, bronchial symptoms, or any other diseases; medications and medical examinations were noted. The mothers were told to bring the infant into the clinic for professional confirmation when tooth eruption was suspected. To simplify the analysis only data collected up to the eruption of the first tooth were analysed. The day that tooth eruption was noted is referred to as day 0 and all data refer to the previous 20 days.

No explanations were given to the mothers as to why they were to check their infants so closely but all were delighted with the special attention. Information from the forms was organised so that the 20 days before the first tooth eruption could be compared. The charts of the patients were re-examined to see if any difference was noted in the 10 days before tooth eruption compared with the previous 10 days as regards fever, otitis media, diarrhoea, cough, and convulsions. The mean daily temperature was calculated and statistical analysis was performed using the χ^2 method.

Results

As expected the first tooth to erupt was a lower central incisor at between 6 and 18 months (mean 8 months). This is similar to the 7·5 month average quoted by Illingworth.[1]

The mean daily temperature was between 36·9°C and 37·1°C from day 19 to day 4. Three days before the tooth eruption occurred the mean (SE) daily temperature increased to 37·14 (0·66) on day 3, 37·2 (0·68) on day 2, 37·4 (0·76) on day 1, and reached its highest value of 37·6 (0·85) on the day the tooth erupted; 95% confidence interval 37·33 to 37·86 (fig 1). On this day, 20 infants had a fever of >37·5°C compared with seven or fewer infants from day 19 to day 4 (fig 2). On the day of eruption 15 had fever of ≥38°C compared with five or fewer infants on days 19 to day 4. Using >37·5°C as the cut off point, this difference was significant at a p value of <0.025 by χ^2. Comparison of days 0 to 9 and 10 to 19 showed 47 *v* 67 days of otitis media, 85 *v* 72 days of diarrhoea, and 52 *v* 58 days with cough; no convulsions occurred.

Discussion

The tendency in the past to attribute serious disease to teething was so prevalent that in 1842 teething was the registered cause of death in 4·8% of all infants who died in London under the age of 1 year and 7·3% of those between the ages of 1 to 3 years according to the Registrar General's report.[2] Although today no such connection is worthy of consideration, the question remains as to whether minor symptoms, especially fever, are associated with teething.

Most texts express opinions without any factual basis. 'There is no definite evidence to support claims of accompanying temporary systemic disturbance. Such disturbance, the most common of which are low grade fever, facial rash and mild diarrhoea are not attributable to eruption of teeth'.[4] 'In the olden days it was a custom to blame teeth for colds, diarrhoea and fever'.[5] An earlier paediatric text in 1907 noted 'there may be a slight fever and restlessness with loss of appetite associated with the eruption of a tooth'.[6]

From the data presented here it would seem that the 'granny's tale' that infants cut their teeth with fever is supported. We would like to stress the danger in attributing fever to teething without ruling out other pathology. Children are teething from about 6 months to 6 years and therefore can easily be found to be teething when ill from other causes. Only the eruption of the first tooth is a clear landmark and so this study limited itself to the period before its emergence. We are intrigued by our finding and have no explanation to offer at this stage for the observation.

We were taught as students to listen to parents; grandma seems also to have had something to tell us.

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Growth patterns after surgery for virilising adrenocortical adenoma

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Abstract

Analysis of growth in nine girls after successful surgical removal of a virilising adrenocortical adenoma showed that five girls continued to grow rapidly for up to 18 months after operation and subsequently had normal growth velocities. The other four girls grew at normal rates after surgery. Only one girl showed progressive advance in bone age after operation and she subsequently had precocious puberty.

Although more than 200 cases of adrenocortical tumour have been described in the literature,[1 2] the natural history of growth and pubertal development after successful surgery has been poorly documented. This paper describes the growth patterns after surgery in nine girls who presented between 1969 and 1988 with virilisation due to adrenocortical adenomas.

Patients and methods

The hospital records of nine girls born between 1965 and 1986 who had successful surgical resection of an adrenocortical adenoma were reviewed. Clinical details of these patients are given in the table. All the subjects were 4 years old or less at the time of diagnosis and five had symptoms for less than three months before presentation. Virilisation with clitoromegaly and growth of pubic hair was present in all cases but two also showed features of Cushing's syndrome; one of the latter patients (case 1) also had hemihypertrophy and was hypertensive at presentation. In all cases the tumours were well encapsulated and apparently complete resection was possible. Tumour weight ranged from 10 to 40 g in all but one case in which a larger tumour (193 g) with some features of a carcinoma was found.

All measurements were obtained using a Harpenden stadiometer and bone age was assessed by two observers using the Tanner-Whitehouse radius, ulna, and short bones (RUS) method. Only reported heights were available for parents. Duration of follow up after surgery ranged from 2·5 to over 20 years (median 10 years).

Results

Information on height and bone age at the time

Initial clinical features and follow up findings in nine girls who had resection of a virilising adrenocortical adenoma in early childhood. Details of reported mid-parental height are also given

	Cases								
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
Features at diagnosis									
Age (years)	3·4	2·7	0·7	4·1	2·5	2·4	1·7	1·6	2·5
Duration of symptoms (years)	1·5	0·5	0·1	0·2	0·8	0·3	0·2	0·3	0·5
Clinical features	V+C	V	V+C	V	V	V	V	V	V
Height (cm)	100·5	89·0	72·0	104·0	94·0	98·4	93·6	81·3	93·6
Height SD scores	+1·0	−0·5	+0·8	+0·7	+1·4	+3·1	+3·3	+0·1	+1·2
Bone age (years)	6·4	4·4	0·7	—	3·2	5·9	4·1	2·0	3·0
Findings at last review									
Age (years)	25·0	18·0	15·0	8·6	12·0	11·0	9·0	3·5	4·7
Height (cm)	178·0	165·0	166·7	132·5	171·0	162·2	142·0	99·5	111·0
Height SD score	+2·6	+0·5	+0·8	+0·7	+3·6	+2·8	+2·0	+0·7	+1·3
Menarche	12·0	14·0	12·4	P	P	P	P	P	P
Last hand radiograph									
Age (years)	7·9	3·7	—	—	10·4	—	8·1	3·5	—
Bone age (years)	8·0	4·3	—	—	10·5	—	10·7	4·0	—
Mid-parental height SD score	NK	+0·9	+1·1	+1·0	+1·7	+1·5	−1·5	+0·5	+1·1

NK, not known (adopted); V, virilisation with clitoromegaly; C, cushingoid; P, premenarcheal.

of diagnosis and height when last reviewed is given in the table. Standard deviation (SD) scores for height are also given, as are the initial bone age findings.

HEIGHT AND BONE AGE AT PRESENTATION

At presentation, the height of all but one girl (case 2) was above the 50th centile and in two girls height was over 3 SD scores above the mean for age. These two cases, who had symptoms of virilisation for three and six months before diagnosis, were inappropriately tall when compared with reported mid-parental height. In five of the other girls who were taller than average, height was in keeping with mid-parental height. Thus, despite evidence of androgen production for up to 18 months before diagnosis, only two girls were inappropriately tall at presentation. Bone age was advanced by more than one year in four girls at the time of diagnosis and in two of these subjects height was more than 3 SD scores above average.

POSTOPERATIVE GROWTH AND PUBERTAL DEVELOPMENT

Two different patterns of growth and adolescent development were observed in the nine girls after surgery. In five (cases 1, 3, 5, 6, 8), rapid growth continued for up to 18 months after operation and subsequent growth velocity was normal, height remaining above the 97th centile in two girls (cases 5 and 6). In the remaining girls growth was at a normal rate after operation with no evidence of deceleration after removal of the tumour.

Adult height is only available in two subjects, who were aged 18 and 25 when last reviewed (cases 1 and 2). Although both girls had significant advanced bone ages when first seen, adult height SD scores were greater than the height SD scores at diagnosis. Four further girls have reached the ages of 9 to 15 years but only one (case 7) has gone on to show evidence of precocious puberty. The girl's bone age was advanced by 2·4 years at diagnosis, and although her postoperative growth rate was normal, bone age continued to advance; at 7·5 years she had stage 2 breast development. She has been treated with cyproterone acetate and has not yet undergone menarche. Five other girls were premenarcheal when last seen, but it is not possible to comment on the pubertal pattern in two of them who were still less than 5 years old.

Discussion

These nine girls showed the typical clinical features of a virilising adrenocortical tumour with clitoromegaly and early growth of pubic hair.[3] While their tall stature at diagnosis suggested androgen induced acceleration of growth, in seven cases reported mid-parental height was above average and in only two was height greater than that expected from mid-parental height.

In most of the early reports on children with adrenocortical adenomas it has been assumed that adult height would be compromised because of advanced bone age at the time of diagnosis.[4 5] However, the above findings do not support this view and it appears that in many girls the prognosis for adult height after the removal of an adrenocortical adenoma may be good, despite the presence of advanced bone age at presentation. While in four of our patients bone age was advanced by more than one year, in all but one case there was a trend for bone age to come back in line with chronological age after surgery. There was no 'catch-down' of growth after surgery and all the subjects grew along or above the centile line achieved at presentation. Thus all the girls have remained tall for the duration of follow up and the two subjects who have reached adult height are taller than might have been expected from their height SD scores at the time of diagnosis.

Precocious puberty after successful removal of a virilising adrenocortical adenoma was reported by Lee *et al* who described two children, both aged 4 years at the time of surgery, with considerably advanced bone ages (9 and 11 years) who developed precocious puberty.[4] In one this occurred at 8·5 years and in the other isosexual pubertal development continued after surgery although virilisation regressed. However, only one of our patients showed a similar pattern of development, with progressive advance in bone age associated with precocious puberty.

In conclusion, the above results indicate that the prognosis for adult height in girls who have had successful surgery for a virilising adrenal tumour may be good despite significant advance in bone maturation at diagnosis. In some patients acceleration of growth continues for some time after surgery but continued advance of bone maturation associated with precocious puberty may be relatively uncommon.

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TYPES OF PSYCHIATRIC TREATMENT

Types of psychiatric treatment: overview

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This is the first of a series of articles on treatment of child psychiatric disorders.

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The aim of this series is to provide paediatricians with information about therapeutic approaches used in departments of child and adolescent psychiatry. Such information can be seen not just as having general educational value. All paediatricians see a high proportion of children with behavioural and emotional disturbances.[1 2] Only a small proportion are referred—many are not because the child psychiatric resources are inadequate, because parents are not motivated, or because the disturbances, although bothersome, are not serious enough. In all these cases the paediatrician may find it helpful to apply some of the ideas described in this series. This may sound like encouragement of dangerous dabbling. But paediatricians are inevitably forced into situations where they try and help families with disturbed children, and providing they proceed with caution, are appropriately self critical, and preferably have the opportunity to discuss what they are doing with a mental health professional from time to time, my observations suggest that they can indeed be extremely helpful.

Definitions

Psychiatric treatment covers all therapeutic approaches used for children with emotional and behavioural disturbances.[3] Types of treatment can be divided into *psychological therapies* and *physical therapies*. Psychological therapies include those that primarily aim to uncover underlying conflicts, tensions, and drives of which the child and family members were previously unaware and which are thought to be the covert source of the problem. These insight promoting therapies are termed *psychoanalytic* if clearly derived from the work of early psychoanalysts, especially Sigmund and Anna Freud and Melanie Klein. The term psychoanalytic treatment is usually reserved for quite intensive (three to five times a week) individual treatment, and it is more likely to be termed psychotherapy or psychodynamic therapy if the underlying concepts are the same but treatment is provided on a less frequent basis. Psychological therapies are termed *behavioural* if they aim to alter what the child or family members do by methods that tackle the symptoms directly, or *cognitive behavioural* if they aim to produce behaviour change by altering patterns of thought. However psychological therapies can also be classified according to the unit (individual, family, group) to which the therapy is applied. Those engaged in family therapy[4] may use psychodynamic or behavioural concepts or a mixture of the two. They may also use concepts special to family therapists. Thus 'systems' therapies are based on the notion that families can be viewed as homoeostatic entities—if you change one part of the system you change the rest.

Physical therapies are less frequently used in children. They include medication, dietary approaches, and electroconvulsive therapy, the last of which is used either extremely rarely or not at all until late adolescence.

Child mental health professionals also provide indirect treatment through consultation without direct clinical contact. *Consultation and liaison work* is carried out especially with paediatricians, social workers, and teachers.

Finally, there is a variety of miscellaneous forms of psychiatric treatment which cannot readily be classified according to the above system. *Hypnosis* aims to allow the child greater control of his or her thoughts and behaviour through techniques employed while the child is in a state of altered awareness.[5 6] 'Holding therapy', particularly used for children with autism, involves forcible physical contact to overcome the withdrawal such children show.

Not so long ago there was considerable antagonism between psychodynamic therapists and behaviour therapists. Psychodynamic therapists saw behaviourism as superficial tinkering that left the real problems untouched. Behaviourists saw psychodynamic therapists as misguidedly applying an unproved set of theories with little interest in or evidence for success. Such mutual dismissiveness has by no means totally disappeared, but there is distinctly more appreciation of the fact that different forms of treatment can be valuable in different circumstances. The indications and contraindications of different types of treatment will be discussed in later articles in this series.

Treatment settings and staff

There is a wide variety of settings in which psychiatric treatment is practised. Community child guidance clinics are now much more commonly termed child and family psychiatric clinics. Child and adolescent departments of child psychiatry may be sited in general hospitals or children's hospitals. Inpatient units usually take either prepubertal children or adolescents, but a minority of larger units admit the entire age range. Some inpatient units also admit a proportion of day patients, and there is a relatively small number of child psychiatric day centres exclusively given over to day patients. Many child mental health staff work in other settings, such as schools for children with emotional and behaviour disorders (EBD schools) and child development clinics.[7]

The professional staff working in any of these centres is likely to be multidisciplinary, and treatment may be delivered by any of the professionals involved. As well as child and adolescent psychiatrists who are medically trained, there are clinical psychologists, educational psychologists (nearly all with teaching experience) and, especially in London and the south east of England, but much less frequently elsewhere, there are analytically trained child psychotherapists. Although many local authority social workers remain in child and family psychiatric clinics and departments, some have been withdrawn and others are mainly taken up with work in child protection and have little or no time for therapy. Although child psychotherapists have a very specialised training in individual psychoanalytic techniques, they are increasingly becoming involved in liaison work and sometimes family therapy. Child psychiatrists and clinical psychologists are likely to be able to apply a range of therapeutic techniques, including most of those described above. In addition, child psychiatric nurses, although most likely to work in inpatient units or day centres, are now increasingly exercising their skills in the community.

Is child psychiatric treatment effective?

This is nearly, but perhaps not quite as naive a question as 'Is paediatric treatment effective?' Although there is an increasing number of studies evaluating effectiveness, recently well summarised for individual psychotherapy,[8] for family therapy,[9] for behaviour modification,[10] and for medication,[11] the indications and contraindications for particular forms of treatment are still sometimes uncertain. There is however good evidence that certain forms of treatment are more suitable for certain conditions than others, as the ensuing articles in this series will reveal.

It must be admitted that some practitioners still enthusiastically apply the same form of treatment to virtually all children and families they see, and this is undesirable. For example, the application of individual psychotherapy to the treatment of autism or medication in the treatment of conduct disorders can be seriously questioned on the basis of existing evidence. Such relatively absolute contraindications can be matched by relatively absolute indications for certain types of treatment. For example, the uses of medication in the severer forms of the hyperkinetic and Tourette's syndrome, of a mixture of individual and family psychotherapy in anorexia nervosa, and of behavioural treatment in nocturnal enuresis and monosymptomatic phobias are well established. However for a variety of other common disorders such as anxiety and depressive states, and conduct disorders, it is likely that non-specific factors such as the enthusiasm of the therapist or therapeutic team are of greater importance than the specific type of treatment employed. Paediatricians in training who find themselves working with psychiatrists and psychologists with different therapeutic orientations may be confused, but should find that they can learn a great deal of value from observing the application of different approaches to similar problems.[12]

As the classification systems employed in child psychiatry become more refined, it is likely that there will be increasing precision in our application of particular types of treatment. In the meantime, it would be highly desirable for evaluative studies to include not only scientifically valid controlled trials, but also measures of consumer satisfaction. With increasing dependence on their 'customers', among whom they must certainly count paediatricians, child mental health professionals will be increasingly sensitive to what their clients think of their interventions.

Indications for referral

Referral to a child psychiatrist or a child mental health service is not really a problematic issue for paediatricians who work closely with their psychiatric colleagues, see them at regular weekly psychosocial meetings and, at least occasionally, at lunch, and who have the opportunity to see which children and families seem to benefit and which do not. For those with less close contacts, some guidelines may be helpful.[13] Children who are functionally significantly disabled by persistent problems that either have no organic basis or an insufficient organic explanation need referral, and the earlier they are referred the better. Some paediatricians have found it helpful to use a screening questionnaire routinely to identify children at risk for psychosocial problems.[14] When from the outset, it is clear that children who present with difficult diagnostic problems probably have a non-organic explanation for symptoms, they should be referred early on, preferably while the investigatory stage is under way, so that when all investigations are proved negative, the child psychiatric department is not seen as a last resort or 'dustbin' department, but the child psychiatrist is seen as someone who has been involved from the start. In the occasional child who turns out to have a rare abdominal tumour or degenerative brain disorder to explain abdominal pains or headaches, the early involvement of a psychiatrist need not antagonise parents if it has been made clear at the outset that the diagnostic process may indeed reveal an organic cause for symptoms. Problematic child protection cases would also benefit from discussion with a psychiatrist, though in many cases direct clinical psychiatric contact will not be indicated.

Of course, probably only a minority of paediatricians are able to refer to psychiatrists as much as they would wish. Paediatricians who press energetically for an increase in their psychiatric service will usually obtain a better service within a reasonable period of time. One hopeful sign for the future is the gradual emergence of a stronger clinical child psychology service, sometimes, as occurs more frequently in the US,[15] working in close partnership with paediatricians. This will not only be increasingly helpful to paediatricians, but will allow child psychiatrists to concentrate more on hospital and community health work for which their medical training has specifically equipped them.

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SPECIAL REPORT

Asthma: a follow up statement from an international paediatric asthma consensus group

The first consensus report,[1] which was the result of a meeting held in December 1988 of a small group of paediatric chest physicians from 17 countries, has had a major impact on paediatric asthma management. The document has been used in many countries as a basis for management protocols, and it has been translated into several languages. In the last two years there have been many new questions but no dramatic advances in either the understanding of the condition or its management. However it was felt appropriate to review the consensus statement in the light of the experience gained in its application throughout the world.

The second meeting, held in July 1991, achieved the same notable accord, this time from 34 delegates representing 22 countries. Several textural adjustments were made and with the involvement of primary care physicians the protocols can be viewed as a complete strategy for the management of children with asthma.

The need for a consensus

Some have questioned the validity of a consensus statement on the management of asthma.[2] Clearly there are many publications in the literature outlining very appropriate management strategies and a consensus statement might be seen as a challenge to experts who have suggested alternative protocols. There has been concern that management which deviated from the consensus recommendations might be viewed unfavourably in legal proceedings, but this is not our intention. However, it must be recognised that consistent delivery of effective and safe care is in the best interests of children with asthma. This is difficult to achieve because of the plethora of conflicting publications on asthma. The prevalence and severity of asthma are increasing, while our understanding of the basic pathology remains incomplete.[3] There are increasing concerns about many of the pharmacotherapies at our disposal, as yet no new drugs have found a place in the management of childhood asthma. The lack of hard data in many areas of management justifies the need for guidelines. The consensus publication is not a set of didactic rules but is intended to aid physicians who are unable to wade through the vast literature of confusing information about virtually every aspect of the condition.

The definition of asthma

The vague definition outlined in the first document has not been changed. This definition was based on a pragmatic approach that asthma was a condition in which episodic wheeze and/or cough occurred in a clinical setting where asthma was likely and other, rarer conditions had been excluded. There has been a strong feeling by some that the concept of eosinophil mediated airway inflammation should be incorporated into the definition.[4]

As we have no information on the pathology in the airway of all but the most severe childhood asthmatics it was not included. However, the need to introduce prophylactic treatment at a very early stage remains a firm recommendation. While this might be seen as synonymous with anti-inflammatory treatment even this has yet to be established.

Community care

A large proportion of children with asthma are managed without recourse to specialised care.[5] There are no absolute criteria for specialist referral, and health systems around the world vary considerably, making general statements about who should care for patients unhelpful. Clinicians must recognise that there are special circumstances which should lower the threshold for referral. Thus the consensus strategies indicate what is required for the patients' effective management rather than who should provide the care. Referral becomes a progressively increasing priority with increasing severity and is mandatory at any stage once the requisite standard of care cannot be met. Communication

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between physicians managing children with asthma has sometimes left much to be desired, leading to conflicting recommendations being made by different doctors about the same patients. Implicit in all the recommendations is the idea that there should be effective communication between doctors and far better medical education for undergraduates and postgraduates. Educational strategies should be evolved for nurses, physiotherapists, and other allied health professionals. Nursery and school personnel require specific additional help in understanding how to handle asthma as it might arise in the school environment.

Diagnosis

The first consensus statement presented two diagnostic algorithms based on the ability of children of different ages to perform simple lung function tests. These have now been combined into one (fig 1). Lung function testing is available at any age but will only be possible in special centres for infants and young children. Furthermore, the younger the child the more likely it is that there may be an alternative underlying cause for recurrent cough and wheeze. Thus there is a greater likelihood that infants will require referral for diagnostic investigation.

The diagnostic scheme starts with a full clinical history and physical examination. Some features strongly support a diagnosis of asthma such as the periodicity of symptoms, nocturnal attacks, seasonal variations, and symptoms produced by allergen exposure or exertion. Associated atopy either in the patient or the family will also support the diagnosis. Under such circumstances a trial of antiasthma treatment can be commenced. In children old enough to perform lung function tests, the response to treatment should be monitored by frequent measurements of peak flow and certainly measurements before and after administration of a bronchodilator. In most cases of asthma where the diagnosis is clear and there is

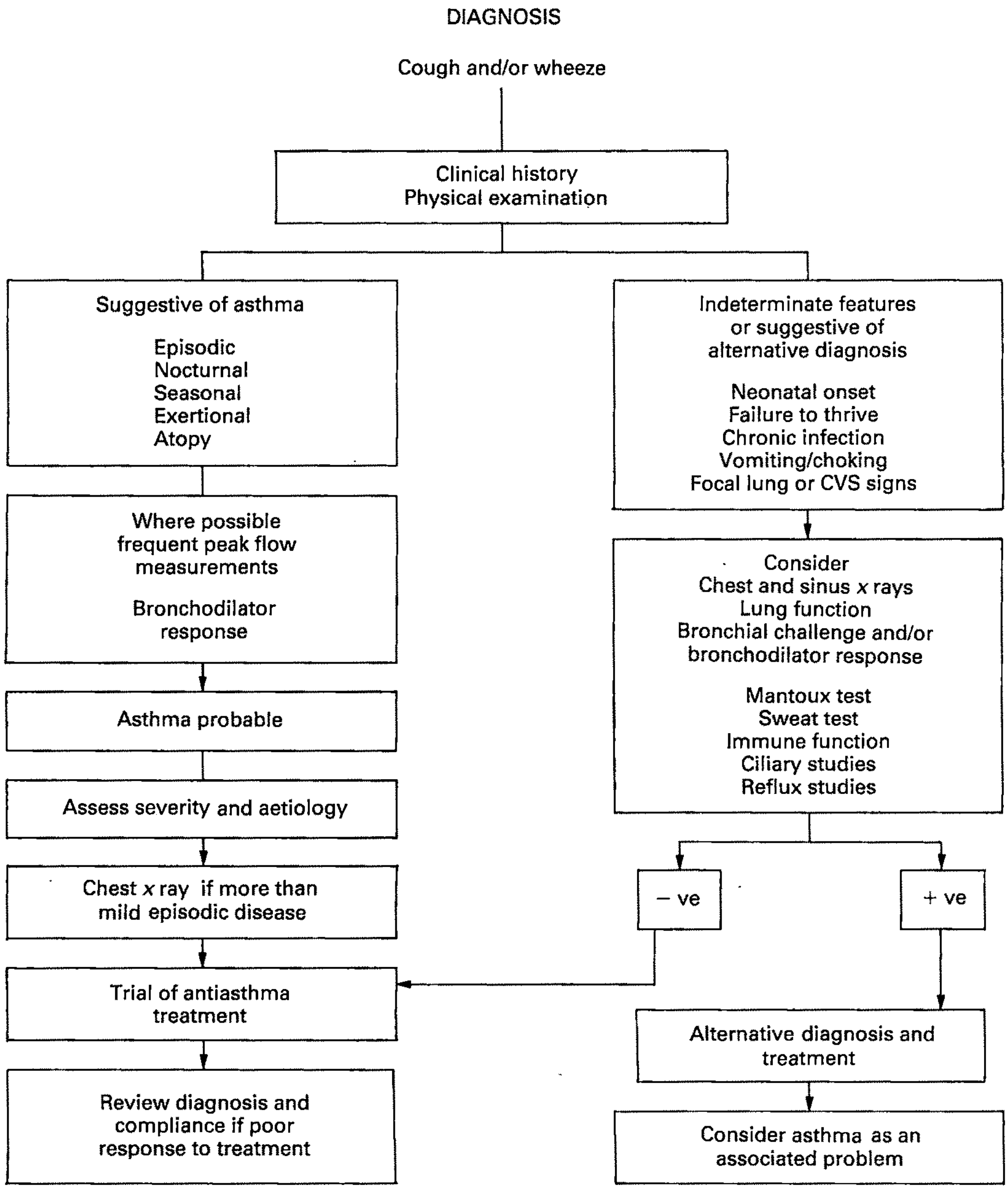
DIAGNOSIS
Cough and/or wheeze
Clinical history
Physical examination
Suggestive of asthma
Episodic
Nocturnal
Seasonal
Exertional
Atopy
Indeterminate features or suggestive of alternative diagnosis
Neonatal onset
Failure to thrive
Chronic infection
Vomiting/choking
Focal lung or CVS signs
Where possible frequent peak flow measurements
Bronchodilator response
Consider
Chest and sinus x rays
Lung function
Bronchial challenge and/or bronchodilator response
Mantoux test
Sweat test
Immune function
Ciliary studies
Reflux studies
Asthma probable
Assess severity and aetiology
Chest x ray if more than mild episodic disease
− ve
+ ve
Trial of antiasthma treatment
Alternative diagnosis and treatment
Review diagnosis and compliance if poor response to treatment
Consider asthma as an associated problem

Figure 1 Diagnostic algorithm for asthma (CVS=cardiovascular system).

an excellent response to treatment, there may be no need for further investigation. However, in all other cases a chest radiograph should be performed to exclude any unexpected alternative pathology. If a response to treatment is poor the diagnosis should be reviewed and the compliance checked before progressing to more potent treatment.

Patients who have a productive cough or apparently recurrent chest infections, a neonatal onset of symptoms, associated failure to thrive, vomiting and choking with respiratory symptoms or focal lung signs, require further investigation. This will include a chest radiograph and lung function measurements before and after treatment. Radiographs of the sinuses, sweat test, tests for immunodeficiency, reflux studies, Mantoux test, ciliary studies, and possibly bronchoscopy may be required. Allergy tests are an aid to diagnosis and are necessary before sensible environmental control measurements can be recommended.

In older children the use of simple lung function tests such as peak flow measurements to record variability over short periods of time, or basic spirometry and responses either to challenge with histamine, metacholine, exercise, cold air or allergen, are worthwhile in diagnosis. In those with subnormal lung function, response to a bronchodilator is equally appropriate.

Assessment of severity

Whereas it is difficult to divide asthma into mild, moderate, and severe categories, no better subdivision exists at present. Categorisation is based on frequency, chronicity, and severity of asthma symptoms. Where possible, lung function measurements will permit a more objective assessment. The response to treatment following the therapeutic algorithms must also be taken into account in the final judgment on the severity. We do, however, need more effective markers of disease activity. Indices such as allergic status, based on skin tests, total IgE and IgE antibodies, bronchial hyperresponsiveness, and the detection of circulating inflammatory markers such as specific cytokines do not yet have a place in routine severity assessment. In adults, increasingly, bronchoalveolar lavage and bronchial biopsies are being performed and the results may well provide information on the severity of disease and indeed on the effectiveness of antiasthma treatment.[6] No information exists to suggest that any of these data can yet be used clinically and research in these areas must be extended.

Mild asthma may be classified as low grade symptoms that do not intefere with sleep and lifestyle, or episodes of cough and wheeze occurring less than once per month. All such episodes should be responsive to bronchodilators taken no more frequently than two or three times per week. Moderate asthma is either discrete attacks occurring no more frequently than once a week or more chronic symptoms not affecting growth or development, in which case sodium cromoglycate prophylaxis is indicated. Patients with severe attacks requiring oral or intravenous steroids or troublesome wheezing on most days or nights are less likely to respond to sodium cromoglycate and will often require inhaled steroids. There are a few patients who fall outside these categories: in particular, patients who have very infrequent but severe or life threatening attacks with completely normal lung function and no symptoms between episodes. This type of patient remains very difficult to manage.

Aims of managment

The goal of treatment should be to allow children to be involved with normal activity, including full participation in exercise and sport. There should not be excessive school absences. Symptoms should not occur by either day or night. Lung function should be normalised with no excess of diurnal variation in peak expiratory flow rate. There should be little need to use relieving doses of β-agonists, preferably less than once every two or three days, and no exacerbations of disease. Adverse side effects of treatment must be avoided, particularly in relation to growth and development. Failure to achieve these goals is indicative of a need to change the treatment.

Co-management: the partnership

Management of asthma is an overall strategy and not just the writing of a prescription. It should not be only patient initiated and involving crisis management but proactive with doctor initiated routine consultation. It has become fashionable to talk about patient self management. However, we should not be asking patients to look after themselves but to manage themselves in partnership with their health professionals.[7] It should be appreciated that day to day management of asthma falls upon the patient and the family and not upon the physician. We, therefore, need to tailor the educational packages and co-management programmes to the individual patient and family. The involvement of appropriately trained practice nurses or physiotherapists in this strategy is particularly important. The objectives are to help the patients and parents as far as possible to develop a complete understanding of the condition, its treatment, and the way to respond to any changes in clinical state. The programme begins immediately the diagnosis has been made, and involves a team approach.

Patients should understand the use of inhaled drugs and peak flow meters, the difference between medications for relief of symptoms and those to prevent episodes. Action plans should be evolved that include instruction on the signs that indicate worsening of asthma and what changes in treatment should be initiated at such times. Thus the four elements of co-management are (i) understanding the condition, (ii) monitoring symptoms, peak flow, and drug usage, (iii) a prearranged action plan, and (iv) written guidelines. A patient diary utilising a traffic signal notation has been found useful in the United States, Australia, and the United Kingdom. Written materials produced by various professional and lay organisations, computer programs, videos, special holidays, and organised sports activities may be of value. Further work is still required to evaluate many of the education materials currently being produced, although some programs have been found to be safe and effective in clinical trials.[8] Ultimately nothing can replace the interaction between patient, family, and health professionals, particularly in addressing psychosocial factors which may make effective disease control difficult.

Environmental control

The role of allergy in asthma management remains one of the more contentious areas. It is widely accepted that the presence of allergy is an important prognostic feature, predicting a more chronic problem. There is also little dispute that allergy is important both in the genesis of the condition and in provocation of symptoms when it is established.[9 10] However, many deny the value of making a specific allergy diagnosis because this has little impact on the management of the condition.

Everyone accepts that environmental tobacco smoke exposure is associated with an increase of symptoms and there is no doubt that this exposure should be avoided at all costs.[11] Reducing house dust mite exposure remains extremely difficult, though there are good controlled trials which have now shown that if mite levels can be significantly reduced symptoms also improve.[12] This, unfortunately, is still not practical in many circumstances. The removal of pets from the home where pet allergy has been established is also important, though it may take many months for the dander to disappear from the dust after removal of the animal.[13] It is possible that the introduction of environmental control in susceptible infants before asthma has developed may become the most effective preventive protocol.[10]

Immunotherapy

Immunotherapy has been established to be superior to placebo in many controlled trials.[14] However, comparison of this treatment with pharmacotherapy in proper controlled studies remains necessary to establish the role of immunotherapy in the management of asthma. There are considerable national variations in attitudes to this treatment and the controversies will only be resolved when larger and more carefully controlled studies are performed. It should only be used when a clear unavoidable allergic trigger has been identified. The treatment should only be initiated by specialists with standardised, characterised extracts. It would appear to be most beneficial in patients with seasonal rhinoconjunctivitis and mild asthma.

Pharmacology

The first consensus document presented four therapeutic algorithms for different ages. These have been simplified and combined into one (fig 2). Thus mild asthma is treated with intermittent β_2-adrenergic agonists, preferably used by inhalation. Once such treatment is required more than three times a week in episodic asthma or where a more severe attack has occurred, there should be a very low threshold for introducing sodium cromoglycate. This should be administered three or four times daily and given a trial of at least six weeks before considering alternative therapeutic agents. Once control is achieved it may be possible to reduce the dose frequency to twice daily. Sodium cromoglycate remains the safest compound developed for the management of asthma and no concerns have ever been raised about side effects. If sodium cromoglycate fails to control the condition and bronchodilators are still required more frequently than three times a week, inhaled corticosteroids should be started. Only the occasional child will require both prophylactic drugs together and compliance is more likely to be maintained if a single prophylactic compound is used.

Inhaled corticosteroids are usually effective in low doses (beclomethasone and budesonide 400 µg/day), though in severe cases higher doses may be necessary. At low doses there is relative sparing from side effects on the hypothalamic-pituitary-adrenocortical axis and growth, but with increasing doses the frequency of side effects also increases.[15]

Side effects may be reduced by the use of a spacer device with metered dose inhaler, which enhances lung deposition while lessening oropharyngeal deposition and systemic absorption.[16 17] After one to two months of inhaled corticosteroids to achieve optimal lung function, it may be possible to reduce slowly the dose to the minimum which maintains good control.

The use of regular inhaled β-agonists more than three times daily has been implicated as a factor contributing to asthma morbidity and deaths.[18] Though not proved, it is prudent where possible to minimise the use of regular β-agonists. However, when moderate doses of inhaled steroid (>600 µg/day) of beclomethasone or budesonide) have failed to control asthma, it may be necessary to consider the use of regular β-agonist treatment including long acting compounds such as salmeterol or formoterol.[19 20] Alternatives may be the use of oral slow release xanthines or inhaled ipratropium bromide.

In very severe disease it will be necessary to increase the dose of inhaled corticosteroid and even to use oral corticosteroids. Under such circumstances the potential dangers of uncontrolled asthma are far greater than any possible side effects that might be produced by the medications. The algorithm demonstrates a progressive increase in treatment with increasing severity of asthma. Some centres recommended an initial 'blitz' approach to achieve maximum response then drawing back to the minimum required to retain this level of function. As yet this can only be recommended for severe asthma.

Inhalation or delivery systems

A single management protocol is now proposed, but it must be adapted for children of different ages, based on their ability to use particular delivery systems (table). More than 50% of children receiving inhalation treatment with a conventional metered dose inhaler have little or no benefit from the prescribed medication because of poor inhalation techniques.[21] Thus the conventional devices cannot be normally recommended for children unless the prescription is accompanied by repeated, thorough, and

Inhalation or delivery systems

Age (years)	*Inhalation delivery system*	*Relieving treatment*	*Preventative treatment*
<2	Nebuliser and air compressor	Salbutamol	
		Terbutaline	Sodium cromoglycate
	Valved spacer and face mask	Ipratropium bromide	Budesonide
2–4	Metered dose inhaler with valved spacer:		
	Nebuhaler (Astra)		Sodium cromoglycate
	Volumatic (Allen and Hanburys)	As above	
	Aerochamber (Forest Pharm Inc)		Inhaled steroids
	FISONair (Fisons)		
	Nebuliser for acute episodes		
5–8	Powder inhalers:		
	Spinhaler (Fisons)	—	Sodium cromoglycate
	Diskhaler (Allen and Hanburys)	Salbutamol	Beclomethasone
	Rotahaler (Allen and Hanburys)	Salbutamol	Beclomethasone
	Turbohaler (Turbuhaler, Astra)	Terbutaline	Budesonide
	Metered dose inhaler with valved spacer	For acute attacks instead of nebuliser	High dose inhaled steroids
>8	Autohaler (Riker; 3M)	Salbutamol	Sodium cromoglycate
	Metered dose inhaler *with training*		
	or powder inhalers	All of the above	

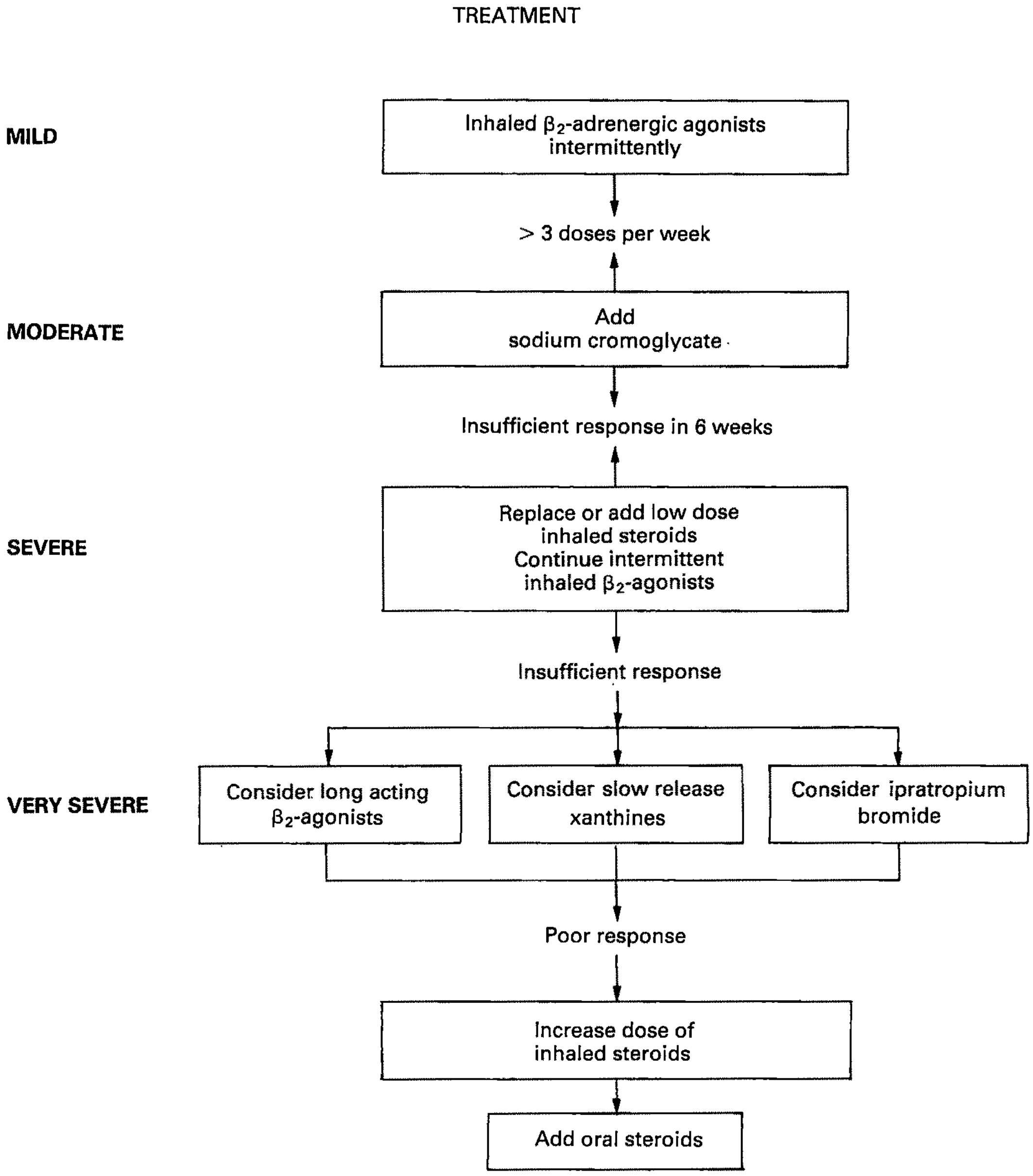
TREATMENT
MILD
MODERATE
SEVERE
VERY SEVERE
Inhaled β_2-adrenergic agonists intermittently
> 3 doses per week
Add sodium cromoglycate
Insufficient response in 6 weeks
Replace or add low dose inhaled steroids Continue intermittent inhaled β_2-agonists
Insufficient response
Consider long acting β_2-agonists
Consider slow release xanthines
Consider ipratropium bromide
Poor response
Increase dose of inhaled steroids
Add oral steroids

Figure 2 Therapeutic algorithm for asthma. This algorithm involves progression to the next step once control is not maintained and both compliance and inhaler technique are optimal.

correct tuition. The use of breath actuated metered dose inhalers will reduce the amount of tuition time required but this should be reserved for children beyond the age of 7 years.[21] The inclusion of a spacer device with a valve system such as the Nebuhaler (Astra), Volumatic (Allen and Hanburys), FISONair (Fisons), Inspir-ese, or Aerochamber (Forest Pharm Inc) allows children of 2 to 3 years or older to use them after effective training, for all antiasthma medications.[22 23] Some younger infants may be able to use a spacer with face mask.[24] During acute wheezing episodes, young children may not be able to move the valve. In such circumstances only nebulisers will be appropriate. The spacer devices reduce oral deposition and swallowed drug and therefore reduce the systemic effects of inhaled steroids while ensuring a good therapeutic response by increasing drug delivery to the airways.[16 17] A good inspiratory effort is required for dry powder systems but all have slightly different optimal inspiratory flow.[21] Thus the lower age limit for the devices will vary. In general, they are most suitable for school age children onwards.

Though nebulisers are expensive, bulky, inconvenient, time consuming, and inefficient delivery systems they are used extensively. Their use is particularly of value in children who cannot be trained to use any other device. In practice this means either children younger than 2 to 3 years or older children with other difficulties and those prone to severe attacks. There are very few controlled studies of nebuliser treatments in this age group; thus our knowledge of dose requirements and optimal nebuliser systems is rather limited.

Recent studies indicate that it is not justified simply to transfer the dose in mg per kg recommended for older children to the younger age group as their inhalation technique, tidal volume breathing, and anatomy of the upper airways are different.[25] In general, a powerful air compressor capable of a dynamic flow rate of 8–10 l/minute and a volume fill of 4 ml in the nebuliser will produce the best output of respirable particles, particularly when using a suspension such as corticosteroids.[26] More work is required to establish the optimal nebulisation techniques for different treatments. Nebulising units (compressor and nebuliser) should be tested before use and at regular intervals (once every 6–12 months) to ensure that they continue to produce respirable particles.

Other drugs

There are currently no adequate data to justify the addition of any other drugs to the general therapeutic algorithm. However, in special circumstances other compounds may be considered. Ketotifen has been shown in some controlled clinical trials to be of benefit in mild asthma mainly in infancy.[27] As it is orally active it at least has the benefit of being easy to administer. Other potent specific histamine H_1 antagonists may have a similar effect.[28]

Nedocromil sodium is now prescribed for mild to moderate asthma in adults and may find a place in the management strategy for childhood asthma. Trials are awaited with interest. In particular, it will be important to establish whether nedocromil sodium has a place between sodium cromoglycate and inhaled corticosteroids.[29]

Long acting β-agonists have hitherto only been available in oral slow release formulations. These have not found a prominent place in asthma management. Two long acting inhaled β_2-agonists have now been formulated: salmeterol and formoterol. Both are now in clinical use in some countries in adult practice. From a paediatric point of view, formoterol has been more extensively investigated.[20] Initial data suggest that there does not appear to be an increase in bronchial reactivity with these compounds and there is even a suggestion that they might have some anti-inflammatory activity.[30] Until more data are available they can only have a limited place in the protocol. Bambuterol is a third medication in the class of long acting β-agonists. It is a prodrug of terbutaline that can be administered orally and has the potential to produce 24 hour bronchodilatation.[31]

There was complete accord among the consensus members about the declining role of theophyllines. The problems of compliance and effects on behaviour mean that it no longer has anything other than a tertiary role in severe asthmatics already on high doses of inhaled steroids.[32] Nevertheless, recent research has identified that phosphodiesterase can be classified into five different groups. Theophylline is a non-specific phosphodiesterase inhibitor affecting all five subgroups of the enzyme. There are two subgroups that may be important in asthma, type III which is bronchoconstrictor and type IV which is proinflammatory. Thus drugs which specifically inhibits type III and type IV phosphodiesterases may have an important role in the management of asthma in the future. A group of drugs known as the isoquinolines are potent type III and type IV inhibitors and are generating interest in research circles.[33]

Potassium channel activators are another very potent group of bronchodilating drugs.[34] So far, however, the haemodynamic effects have not been disassociated from those of bronchodilatation. The diuretic, frusemide, has been shown to have some bronchodilator and induced asthma blocking effects by inhalation in that it prevents both exercise induced and adenosine induced bronchoconstriction.[35] It is possible that it has a similar mechanism of action to sodium cromoglycate in the airways but this requires further elaboration.

It is too early to say whether the newer inhaled steroids are going to be a significant advance on those already available. There is no place for them in the protocols at present. The role of methotrexate, cyclosporin, oral gold, and other immunomodulatory drugs remains to be established even in adult asthma.[36 37]

Acute severe asthma

The management of acute asthma has undergone some evolutionary changes (fig 3). The importance of oxygen in all cases of acute

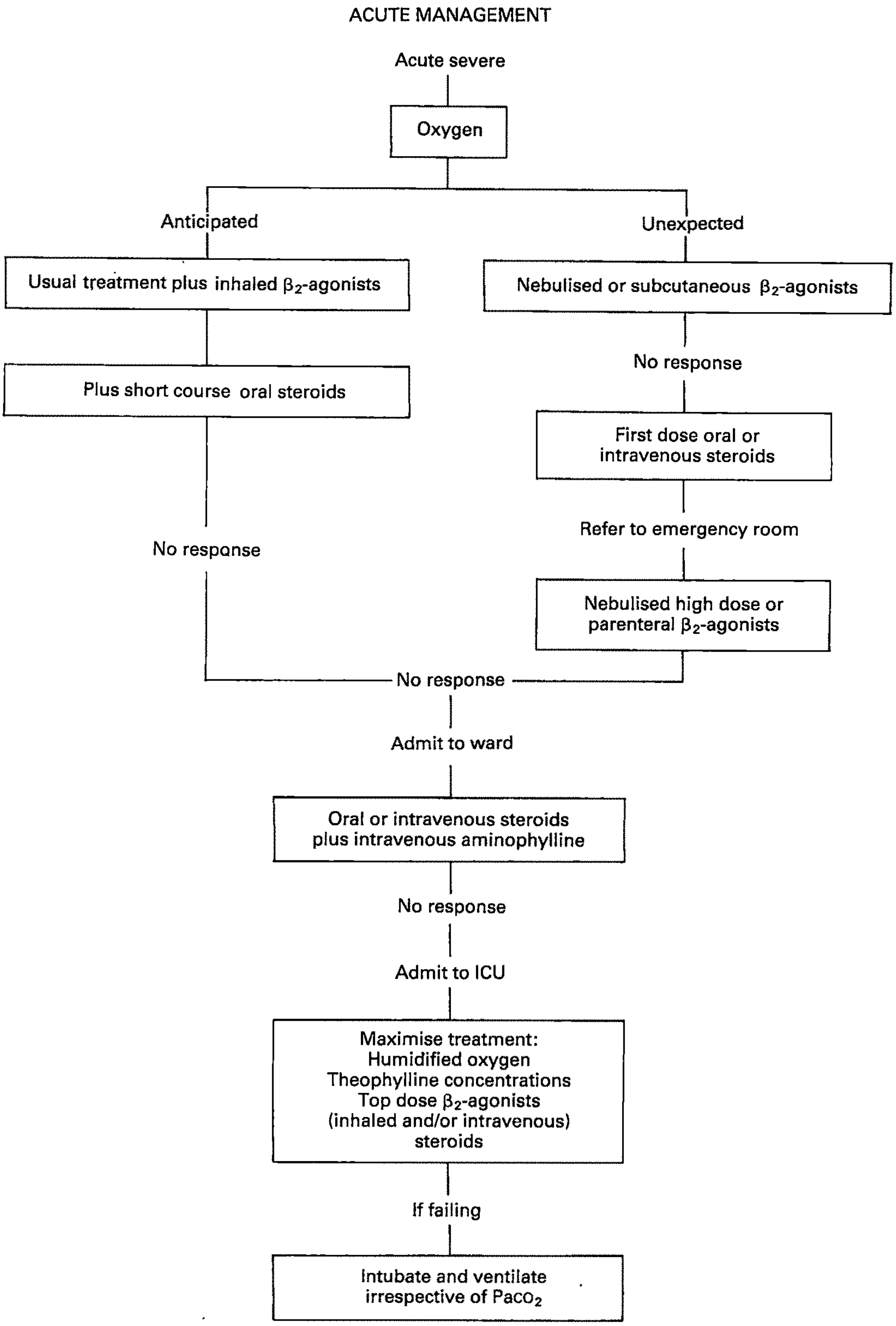
ACUTE MANAGEMENT
Acute severe
Oxygen
Anticipated
Unexpected
Usual treatment plus inhaled β2-agonists
Nebulised or subcutaneous β2-agonists
Plus short course oral steroids
No response
First dose oral or intravenous steroids
Refer to emergency room
No response
Nebulised high dose or parenteral β2-agonists
No response
Admit to ward
Oral or intravenous steroids plus intravenous aminophylline
No response
Admit to ICU
Maximise treatment: Humidified oxygen Theophylline concentrations Top dose β2-agonists (inhaled and/or intravenous) steroids
If failing
Intubate and ventilate irrespective of Paco2

Figure 3 Algorithm for management of acute asthma (ICU=intensive care unit, Paco$_2$=arterial carbon dioxide tension).

asthma at concentrations that achieve adequate oxygenation requires emphasis, as do the indirect means of measurement of oxygenation and ventilation (for example, pulse oximetry, transcutaneous capnometry) which are now widely available and should be freely used in this setting.[38] Inhaled β-agonists can be used in far higher doses and for longer periods than had been hitherto recommended, including continuous administration of full strength respirator solutions of salbutamol and terbutaline,[39] though this should be done only in a hospital setting.

The criteria for resorting to ventilation cannot be easily defined. At this point there must be serious reservations about the applicability of the Downe's criteria, with their heavy reliance on arterial carbon dioxide tension. Current management dictates that arterial blood gases alone are inadequate: on some occasions it is entirely appropriate to manage patients without ventilation even with a high arterial carbon dioxide tension, but only if effective treatment is about to be instituted. If there is no beneficial response in terms of increased alveolar ventilation, mechanical ventilation under sedation and neuromuscular blockade should be started. Conversely, there are other occasions when a patient is obviously failing clinically even when the arterial carbon dioxide is relatively low, or when it is still quite low but rising despite maximal treatment having been instituted, and mechanical ventilation is required immediately.[40]

The protocol starts from the use of nebulised β_2-adrenoceptor agonists diluted in normal saline with continuous humidified oxygen. The dose of β-agonists can be repeated frequently, given in multiple breaths of full strength solution, or even given continuously (see above) where appropriate electronic monitoring is available. However, failure to respond to this treatment indicates the need for intravenous salbutamol, or either subcutaneous terbutaline or adrenaline, and oral or intravenous corticosteroids. Appropriate doses of hydrocortisone are 4 mg/kg and prednisolone 1–2 mg/kg, both every six hours. It is no longer appropriate to administer intravenous aminophylline in a home setting but it may be used in hospital in the conventional protocol of a loading dose of 6 mg/kg of aminophylline over 10–20 minutes followed by 1·0 mg/kg/hour continuous infusion, with close monitoring of serum theophylline concentrations in order to keep the values between 10–20 μg/ml.

Clinical trials

As with the previous consensus meeting, more questions than answers were raised in relation to virtually all the areas of management of asthma. There is still a need for basic, well controlled clinical trials. The most important prerequisite is complete characterisation of the population of the patients entered into the trial. Asthma has many forms and studies must involve as homogeneous a population as possible. Thus atopic status, disease severity, age, and physiological variables must, as far as possible, be described. As the disease can be enormously variable long term trials are preferred, covering a period when the patients are most likely to have clinical problems.

The environment will have a strong influence on manifestations and this requires characterisation. Adherence to the treatment during a trial is always difficult to assess, but, with the advent of programmable inhalation devices this may become an important part of the assessment. The mode of inhalation, the characteristics of the delivery system, and the doses delivered must also be standardised.

There are problems in determining outcome. Much of the assessment is based on subjective recording of symptoms but where possible physiological measurements should also be made. Twice daily peak flow measurements are usually employed but their value has been limited. Recently, diary card assessment of some symptoms has been shown to be unsatisfactory and for instance correlates very poorly with objective recording of night cough.[41] Measurement of bronchial hyperresponsiveness has been extensively employed but it has yet to be established whether this provides any indication of the severity of the underlying disease process. It is not yet considered ethical to do fibreoptic bronchoscopy, bronchoalveolar lavage, and bronchial biopsy in clinical trials in childhood. In longer term trials it is imperative to utilise measures of general health, growth, and development.

Statistical analysis comparing large groups of patients on active or placebo treatment has become the essential prerequisite for publication of a clinical trial. A statistician must be involved at the outset, during the design of a study. However, it is also important to appreciate that sometimes individual differences might be missed in the analysis. It may sometimes be appropriate to subdivide the patient groups for further analysis, as some drugs may only work on very restricted categories of patients. High placebo responses make control essential in most studies.

Clinical trials are often conducted jointly between clinicians and the pharmaceutical industry. Such studies should be analysed independently and submitted for publication irrespective of the results. The data must be available to all parties at an agreed time. Sponsorship should be acknowledged in the publications and the use of trial results for marketing and advertising should be based on published data and by agreement between the participants. Unpublished trials should not be used in advertising material. Where a multicentre trial is conducted, one clinician should be selected to act on behalf of all the medical participants, to ensure a totally ethical approach.

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4. Sampling distributions

M J R Healy

In note 2 of this series I have described the sort of statistical reasoning that underlies significance testing. While estimation is of far more practical importance, it will have been seen in note 3 that the construction of confidence intervals is very closely tied up with the ideas of significance testing—effectively, a hypothetical value for a population parameter is inside a confidence interval if its use in a null hypothesis renders the data non-significant at an agreed level. It may be of interest, then, to describe in a bit more detail just how significance probabilities are arrived at.

To take a simplistic example, suppose we have a sample of rectal temperatures taken on 20 healthy babies and that we adopt as a null hypothesis the assertion that the mean temperature in the population from which the sample is drawn is 37·0°. The mean of the 20 sample values is (say) 37·3°, a deviation of 0·3° from the hypothetical value. What is the probability of getting a deviation as large as this?

We can approach the question by doing a thought experiment. We have a hypothetical population of temperatures with a mean of 37·0°. Imagine that we draw a very large number of samples of size 20 from this population and calculate the mean of each of the samples. By doing this, we are constructing a quite new population. Its items are samples of 20 and its variate is the mean of each sample. Our actual data provide us with a single item from this new population with a variate value of 37·3, and what we need is the probability of obtaining a variate value as extreme as the one we have actually observed. We could get this if we were to know the probability distribution that describes our new population. This distribution is known as the *sampling distribution* of the sample mean. The original distribution of individual temperatures is called the *parent distribution*.

Statistical theory tells us several things about the new distribution. To begin with, if the parent distribution is Normal, then the sampling distribution of the mean will be Normal also. However, a remarkable result, known to statisticians by the mysterious name of the central limit theorem, states that the shape of the sampling distribution of the sample mean comes rapidly closer to that of a Normal distribution as the sample size increases, almost irrespective of the shape of the parent distribution from which the individual data values were drawn. This is one reason for the key part played by the Normal distribution in statistical practice.

Naturally enough, the parameters of the sampling distribution are related to those of the parent distribution and statistical theory provides some details. For a start, the means of the two distributions are the same, irrespective of the shape of the parent. This says that, on average over a long sequence of samples, the sample mean is equal to the population mean. In the jargon, as an estimate of the population mean, the sample mean is *unbiassed*.

A second theoretical result states that the variance of the sampling distribution of the mean (the square of its standard deviation) is given by the variance of the parent distribution divided by the sample size. In other words, if the standard deviation of the parent distribution is σ and the sample size is n, the standard deviation of the sampling distribution of the mean is $\sigma/\sqrt{n}$. This in turn tells us the extent to which the mean of a sample is less variable than a single observation; it is a quantitative version of what is loosely referred to as the law of averages. For brevity, the standard deviation of the sampling distribution is usually called the *standard error* of the estimate in question.

Returning to our original question, the mean of our (hypothetical) parent distribution is 37·0°, so this is also the mean of the sampling distribution of the mean. Just for the moment, pretend that we know that the standard deviation of the parent distribution is 0·5°. Then that of the sampling distribution (the standard eror of the sample mean) would be $0{\cdot}5/\sqrt{20}=0{\cdot}112°$. The observed sample mean of 37·3° deviates from the mean of its sampling distribution by an amount of 0·3°, and this is equal to $0{\cdot}3/0{\cdot}112=2{\cdot}68$ standard errors. From a table of the Normal distribution, the probability of a deviation as large as this (in either direction) is 0·0074; this is the significance probability we are seeking.

. . . or it would be if we had the knowledge we pretended we had about the standard deviation of the parent population. In practice we almost never have such knowledge—just as with the mean, we have to form an estimate of the standard deviation based on the values in the sample. We can postpone for the moment the details of how this is done; suppose that the result is an estimated standard deviation $s=0{\cdot}48°$, say (note the use of the italic letter s to distinguish the estimated quantity from its population counterpart σ). The estimated standard error of the mean is now $0{\cdot}48/\sqrt{20}=0{\cdot}107°$ and the observed deviation amounts to $0{\cdot}3/0{\cdot}107=2{\cdot}80$ *estimated* standard errors. This

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is slightly larger that before, when we were pretending that we knew the population variance, but this may, of course, be a chance effect—it is quite possible that the estimate of the population standard deviation calculated from our sample is by chance smaller than the true value. To allow for this, we look up the probability, not in the table of the Normal distribution, but in that of the quantity t introduced by Student (the modest pseudonym of W S Gossett, head brewer at Guinness's Park Royal brewery). The probability corresponding to 2·80 standard errors in the Normal distribution is 0·0051; in the table of t, assuming a sample of size 20, it is distinctly less extreme, at 0·0113.

A very large number of statistical questions can be answered by extending the sort of argument we have used above. Essentially we start with a quantity (such as a sample mean, or the difference between two means, or a regression coefficient) which has, at least approximately, a Normal sampling distribution. We calculate the deviation of this quantity from some hypothetical value (often zero). We estimate from the data the standard deviation of the parent population and from this we derive the estimated standard error of the quantity we are using. We can then calculate t as the deviation divided by its estimated standard error and look this up in the appropriate tables.

Two subsidiary issues can be conveniently taken up here. First, how do we go about estimating the population standard deviation from the sample values? The population variance (the square of the standard deviation) is defined as the average value over the population of the squared deviations from the population mean—in symbols, the average of $(x-\mu)^2$ where x stands for a variate value and μ for the population mean. It is tempting to estimate this by taking the average over the sample of the corresponding sample quantities, $(x-m)^2$ where m stands for the sample mean. There is an oddity here, though. It can be shown quite easily that the straight average of $(x-m)^2$ is smaller than that of $(x-a)^2$ for any other value of a. In particular, we can be sure that the straight average of $(x-m)^2$ is likely to be smaller than that of $(x-\mu)^2$, even though we do not know what μ is!

This tendency to underestimate can easily be counteracted though. Instead of dividing by n, the sample size, when forming the average, we divide by $(n-1)$. This divisor is called the *degrees of freedom* of the estimated variance.

Some of the magic can be stripped from this divisor by noting that the sum of the deviations from the sample mean $(x-m)$ is *exactly* zero. This means that if you tell me $(n-1)$ of the deviations, I can tell you the last one without looking at the data. Once the sample mean has been calculated, there are only $(n-1)$ pieces of independent information left. The difference between dividing by n and $(n-1)$ is not considerable except in very small samples, but there are more complex situations where the degrees of freedom differ more markedly from the sample size and the concept is an important one. The facility provided by some calculators for dividing by n rather than by $(n-1)$ (also advocated by some textbooks when the sample size exceeds some entirely arbitrary limit) should be avoided—why bother whether your sample is 'large' or 'small' when one method is correct for both?

The second topic relates to the important distinction between the standard deviation of the parent population (the SD) and that of the sampling distribution (the standard error or SE). Both can be useful and each can be calculated from the other, but in preparing a scientific paper it is helpful to the reader if each one is quoted where it is appropriate.

The SD is a quantity that describes the variability of the parent population. It is thus usually needed in the 'subjects and methods' section of a paper. If the study involves two or more groups of patients, the reader will wish to be assured that the groups are comparable in their baseline data, and this comparability should include variability as well as mean values.

The SE on the other hand is related to the sample mean and is a measure of its precision. It is used as described above in assessing the significance of differences between the sample mean and a hypothetical value (or between two sample means). It will therefore usually be appropriate in the 'results' section of a paper and the associated tables and diagrams. The choice between quoting the SE and related confidence intervals has been discussed in my note 3.

Whether the SD or the SE is being quoted, it is extremely important to make it clear to the reader which is being used. The ± sign by itself is far too ambiguous (it may even indicate a confidence interval) and should not be used.

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LOOKING BACK

Decline and fall of the tubercle bacillus: the Newcastle story 1882–1988

F J W Miller, Mary D Thompson

In 1882, when Koch isolated and cultured the turbercle bacillus, Newcastle upon Tyne was a city of 160 000 people. A century earlier the population had been about 30 000 and in that time prosperity founded upon the export of coal, the manufacture of glass and chemicals, the production of armaments, and the building of ships for both peace and war had encouraged immigration not only from the surrounding countryside and other parts of England but also from Scotland and Ireland. Work was plentiful and rapid growth had produced areas of great contrasts and poor property.

Newcastle 1882–1913

By then the first medical officer of health, Dr H E Armstrong, who had come to that appointment from six years as the resident medical officer of the Newcastle dispensary had been in office nine years. His years at the dispensary had certainly given him intimate experience of the disease patterns and the conditions of life for many families and their children. Not only a tough Northumbrian he was also long lived and from 1873 to his retirement in 1913, while he waged war against disease, he also produced a series of annual reports revealing how Newcastle with other industrial cities suffered death rates well above those for the country as a whole and that infant and child mortalities were particularly high. Fortunately his reports were continued by his successors until 1972 and today make fascinating reading.

Using these reports we have tried to trace the toll which *Mycobacterium tuberculosis* exacted during that time. Dr Armstrong had many difficulties. Statutory notification of tuberculosis was still 30 years in the future and information came chiefly from death certification and the tables produced by the Office of the Registrar General. Deaths from tuberculosis were then noted under the heads of phthisis, tabes mesenterica, scrofula, in addition to tuberculosis. Before 1882 there could not have been any bacteriological evidence and after that date it must have come slowly. Even so the numbers of deaths returned as due to phthisis were probably understated for there was considerable family opposition to the term as tuberculosis was widely thought to be a hereditary trait. But we show in table 1 the deaths from tuberculosis as recorded in Dr Armstrong's reports covering a period of 30 years before notification.

During that time although Henry Armstrong became more and more concerned about tuberculosis, he could not measure its prevalence and, as he lacked access to the community, he could not mount a study. But, in 1895, he arranged for the examination of samples of the milk entering the city or produced within it. Some 10% of those examined contained viable tubercle bacilli and he encountered great difficulty in getting any effective action in respect of the cattle concerned. Yet he knew that most deaths were due to pulmonary tuberculosis and the chief spread was from person to person. In 1907 he made tuberculosis the subject of a special report to the sanitary committee discussing its causes, its toll, and its control.[1] In his annual report for the same year he pleaded for a scheme of local and national treatment and prevention asking for: (1) compulsory notification of tuberculosis. (2) The provision of sanatoria, hospitals, and dispensaries. (3) Methods to prevent infection of the lungs and abdominal tract. (4) The education of public opinion. (5) That legal powers should be granted to sanitary authorities to carry out the above four measures. (6) The establishment of a national health authority.

Four years later in 1911, when the first National Insurance Act created the 'panel' for the medical care of employed men, a duty was placed on local health authorities to establish a tuberculosis dispensary and to keep a register of notified cases (partial notification had started in 1909). For the first time also a specific disease, tuberculosis, was named in a general act of parliament and the sum of sixpence (2·5p) per insured person was set aside for treatment. No provision was made for wives or families. Notification was not obligatory for all types of tuberculosis until 1 January 1913. In that year despite the reluctance of many doctors in practice, no fewer than 972 cases of pulmonary tuberculosis were notified in Newcastle, 326 persons were certified as dying from phthisis, and 153 from other forms of tuberculosis, a death rate of 1·76 per 1000 inhabitants, half the

Table 1 Newcastle upon Tyne 1875–1905

	Deaths from tuberculosis			
	1875	*1878*	*1901*	*1905*
Total	491	539	596	608
Rate/1000 population	3·6	3·7	2·8	2·3
Age <1 year	73	56	34	54
Age <5 years	120	128	115	139

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rate of 35 years earlier. Dr Armstrong's last report before retirement also concentrated on tuberculosis and the measures required under the 1911 National Insurance Act and he was quite explicit that the local resources were not sufficient for local requirements. The city had arranged for the use of 30 beds at a sanatorium for adult patients and also for the same number of beds at a children's sanatorium. Both institutions were controlled by voluntary associations.

Treatment 1913–45

Dr Armstrong was succeeded by his friend and colleague Dr Harold Kerr who was equally keen to implement the 1911 act. In 1913 a doctor was appointed to organise the tuberculosis dispensary and to compile the register of notified cases. The beds at both the sanatoria were already filled and in addition 14 beds for 'advanced cases' had been made available and 60 more planned at the large City Hospital for Infectious Diseases. The belief was that rest, fresh air, and good food produced the best conditions for healing. Although the amount of sanatorium and hospital treatment increased steadily, that in essence was the treatment available for the next 30 years. But natural healing in tuberculosis is slow and for many the time was all too short.

Attempts were certainly made to simulate sanatorium conditions at home but were impossible to attain on any scale. Public understanding of tuberculosis was limited and many believed it was a family constitutional disease. Many people lived in poor overcrowded houses, illness meant loss of employment and difficulty for re-employment. Families could not be supported by husbands or cared for by mothers. Support available through voluntary aid was variable. Although tuberculosis of the lungs claimed most attention, many people young and old had other forms of the disease affecting bones or joints, lymph nodes, or the central nervous system. Healing often left permanent deformity and handicapped 'hunchbacks' were familiar sights.

Table 2 Newcastle upon Tyne 1885–1972. Deaths and deaths rates from tuberculosis/1000 population

	Pulmonary		*Other (central nervous system, etc)*		*Total*		*Population*
	Deaths	*Death rate*	*Deaths*	*Death rate*	*Deaths*	*Death rate*	
1885	368	2·28	138	0·86	506	3·13	161 526
1895	406	2·05	218	1·10	624	3·15	198 141
1905	397	1·56	211	0·83	608	2·38	255 160
1913	326	1·20	153	0·56	479	1·76	271 295
1915	380	1·37	162	0·58	542	1·95	278 107
1925	343	1·20	101	0·35	444	1·55	286 300
1935	240	0·82	63	0·22	303	1·04	292 700
1940	251	0·98	51	0·20	302	1·18	255 900
1945	227	0·85	47	0·18	274	1·03	265 990
1950	183	0·62	25	0·08	208	0·70	294 800
1955	48	0·17	4	0·01	52	0·18	281 000
1960	24	0·09	4	0·015	28	0·10	268 970
1965	19	0·07	6	0·023	25	0·10	257 460
1970	9	0·04	3	0·013	12	0·05	236 730
1972	10	0·045	2	0·009	12	0·05	217 220

Table 3 Notifications of tuberculosis in Newcastle upon Tyne 1915–75

	Notifications of tuberculosis			
	Pulmonary cases	*Other types*	*Total*	*Attack rate/ 1000 population*
1915	612	352	964	3·46
1925	546	303	849	2·9
1935	464	176	640	2·2
1945	580	115	695	3·0
1955	373	68	441	1·57
1965	142	32	174	0·67
1970	82	17	99	0·42
1975	61	17	78	0·35

Many of the large cities, including Newcastle, had death rates greater than the country as a whole and in the 1920s and 1930s the Tyneside boroughs including Newcastle had the highest death rates in the country. Within Newcastle the poorer wards had much higher death rates than the more fortunate areas.[2] During those years Newcastle had increased the number of beds available to more than 100 for pulmonary disease and 60 for other types and still maintained the 30 beds in the children's sanatorium. Children were also admitted to the various hospitals in the city. Those levels of provision continued until the mid 1940s.

The pathogenesis and epidemiology of tuberculosis in Newcastle

The numbers of deaths from tuberculosis were recorded each year in the medical officer of health's reports and notifications since 1913 (tables 2 and 3). The phenomenon of tuberculin sensitivity had been demonstrated by Koch and Mantoux but the natural history of the complex relationship between man and the tubercle bacillus had not been established despite Marfan's acute clinical observation in 1886 that persons with well healed scars from tuberculosis of the cervical lymph nodes were not likely to suffer from pulmonary tuberculosis.[3] In 1912 Anton Gohn had described calcified well healed pulmonary foci and their related nodes but that was a pathological rather than an epidemiological observation.[4] In 1929 and later Rich and McCordock studied tuberculin sensitivity and its effects,[5] and their studies were soon followed by Blacklock's report on the pathological findings of tuberculosis in children.[6] But there was no agreement concerning the relationship between primary infection and disease in adults and regrettably there was a tendency to regard primary infection as both inevitable and innocuous.

Studies to ascertain the prevalence of tuberculous infection at different ages using the tuberculin test seemed long in coming and as far as we can tell the first study for that purpose in this country was in 1929 when Hart tested children and young adults attending the outpatient department of the London Hospital.[7] Those tested had no signs of tuberculosis and were attending for other reasons. That study showed the incidence of primary infection rose steadily with age and that, by 21 years 95% of those examined gave positive results (table 4). Twenty years later the Medical Research Council survey showed that two of every three people aged 19–20 tested in northern urban areas were tuberculin positive and that the annual infection rate appeared to be about 3%.[8] In Newcastle, in the 1000 family study, which began in 1947, 7·2% of children were tuberculin

Table 4 The incidence (%) of positive tuberculin sensitivity at ages to 21 years

The London Hospital		*Northern urban areas*	
Ages	*Hart (1929)*[7]	*Ages*	*Medical Research Council (1949–50)*[8]
0–2	6·5	5–6	15·2
3–5	18	7–8	21·3
6–10	38	9–10	29·5
11–20	70	11–12	36·5
21	95	13–14	42·5
		15–16	51·0
		17–18	59·0
		19–20	67·5

positive at 5 years in 1952 and 12·3% at 13 years in 1960.[9]

In tables 2 and 3 we have shown the mortality from tuberculosis as given in the medical officers of health's reports from 1885–1972 and notifications from 1915–75. The period relating to death, covering almost a century, can be divided into three phases. During the years 1885–95, although the numbers of deaths increased, the death rate did not change as the population increased. Then, from 1905, the death rate, except for the years 1914–18, slowly decreased until 1945. During that period the great majority of children had experienced a primary infection before 20 years of age and there must have been plenty of opportunities for reinfection. The capacity of the individual to withstand the development or to heal clinical disease depended upon their own powers of resistance which in turn depended upon nutrition, the frequency of other infections and illnesses, and their habit and conditions of life. So despite years of economic depression, unemployment, much poor housing, ignorance of or failure to take reasonable health care, the conditions of life for many or most of the people must have slowly improved. In the 35 years from 1905–40 the death rate from pulmonary tuberculosis fell by a third and for other forms of tuberculosis by three quarters.

But it was between 1945 and 1950 that the 'decline' became the 'fall', which was even more headlong between 1950 and 1955 and thereafter. Notifications of new cases showed the same general pattern although the rate was not so great. Figure 1 shows the rates of fall of death rates from tuberculosis of all types, from pulmonary tuberculosis and from other forms. Figure 2 shows the changes in attack rates from 1915 to 72. The data are those given in tables 2 and 3. The non-respiratory tuberculosis comprised abdominal tuberculosis (tabes mesenterica), tuberculous meningitis, and generalised or miliary tuberculosis; bone tuberculosis was not often given as a cause of death apart from a general spread. Although pulmonary tuberculosis or phthisis was sometimes given as a cause of death in young children, those terms represented, by and large, the deaths of adolescents and adults. Deaths in the pulmonary groups could have been the result of a progressive primary infection particularly in adolescents and young adults but later would have been due either to reinfection at a time of lowered resistance or to reactivation of an old primary lesion.

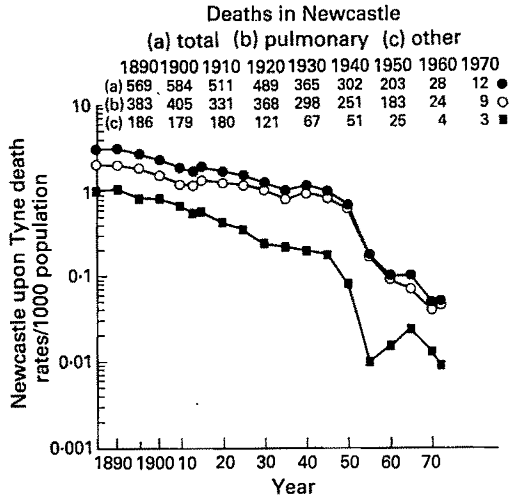

Figure 1 Death rates/1000 population for tuberculosis in Newcastle upon Tyne, 1885–1975. (Total deaths from all causes 1885–1952 was 28 515.)

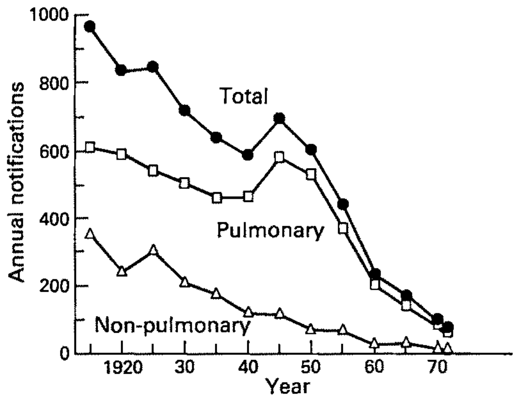

Figure 2 Notification of tuberculosis in Newcastle upon Tyne in 1915–72.

Reference to table 1 and fig 1 will show that the death rate from pulmonary disease fell more slowly than that from non-pulmonary disease. We know that the majority of children were still getting primary infections. Certainly the numbers of children in the population were diminishing and death rates from infective causes were declining but the average heights and weights of children in maintained schools were increasing both in girls and boys.[10] These trends give some support to an overall improvement in health and therefore of resistance to primary infection. To examine that possibility further we have tried to calculate the fall in death rates for children up to 15 years of age compared with the older population from 1885–1960 (table 5). From these figures it would seem that the death rates in children certainly improved faster than those over the age of 15 years and would support the impression gained from fig 1. By 1960 deaths of children from tuberculosis had ceased to occur in Newcastle. During the war years 1939–45 notifications of pulmonary tuberculosis increased but that was at least partly due to the work of the mass miniature x ray units. Deaths from pulmonary tuberculosis continued to decline as did notifications and death rates of non-pulmonary disease.

That long period of decline was to be

Table 5 Newcastle upon Tyne 1891–1961. Deaths from tuberculosis in children to 15 years and people thereafter

	Population (1000s)		*Deaths from tuberculosis*		*Rate/1000*	
	$\leqslant 15$	*>15*	*$\leqslant 15$*	*>15*	*$\leqslant 15$*	*>15*
1891–1900	73·8	139·7	211	415	2·85	2·96
1901–10	80·0	174·3	190	378	2·3	2·16
1911	86·0	181·2	154	353	1·79	1·95
1921	83·8	194·6	111	340	1·32	1·74
1931	85·7	197·3	73	324	0·85	1·64
1941	64·0	190·9	31	259	0·48	1·35
1951	66·2	226·0	4	120	0·06	0·53
1961	63·4	206·0	0	28	—	0·13

Population data and deaths from tuberculosis are annual averages taken from the Registrar General's decennial reports of 1891–1990 and 1901–10.
Population data 1911–61 from census returns and deaths from tuberculosis from the annual reports of the medical officer of health.

succeeded by the near miracle of the fall. The success of the sulphonamides and penicillin had stimulated research and by 1944 Waksman working in Ann Arbor had prepared streptomycin sulphate and found it active against tubercle bacilli. Some years earlier Lehmann in Sweden had shown paraminosalicylic acid also had an effect on tubercle bacilli. Together these preparations were the agents which brought the initial changes and reinforced by isonicotinic hydrazide in 1950 made an effective cure available. Although there were many lessons to be learned and new drugs were required, the whole attitude to tuberculosis was changed and the possibility of its elimination from the community became a realistic objective.

Tuberculosis in children

We have shown the death rate from tuberculosis in children had been declining. But, in 1945 the bacillus was still an important cause of death accounting for 15% of deaths of children aged 1–15 years in England and Wales and between 1939 and 1947 in Newcastle it killed more children of that age than any other cause (table 6). Also in Newcastle children formed a higher proportion of all deaths from tuberculosis than those in at least one London borough (table 7). Those deaths were certainly associated with primary infection although its risks had not been quantified and sometimes hardly admitted.

In 1941, in an attempt both to help families and to obtain data a 'clinic' was organised where young children who had been or were in contact with notified cases of tuberculosis could be seen and examined.[11] It was held in the children's department of Newcastle General Hospital because it was felt that children would be brought there more readily than to a tuberculosis dispensary. The parents or relatives bringing the children were counselled and their anxieties met as far as possible, the children were examined, tuberculin tested, and thereafter seen at intervals or when parents wished. In that way general advice could be given, tuberculosis could be explained, and data gradually accumulated. Information regarding all young children in contact with new notifications of tuberculosis was sent to the child welfare department of the city whence the clinic was organised and the families visited.

Table 6 Newcastle upon Tyne 1939–47. Deaths of children 1–15 years

	Age (years)	*Acute respiratory disease, measles, pertussis*	*Tuberculosis*	*Diphtheria*	*Total (all causes)*
	1–5	187	106	68	497
	>5–15	30	136	59	523
Total	1–15	217	242	127	1020

Table 7 Deaths from tuberculosis 1942–45

Place	*Population*	*Deaths from tuberculosis*			
		All ages	*0–5*	*>5–15*	*0–15*
Ealing and Acton	212 000	450	13	5	18
Newcastle	270 000	1177	58	72	130

Fortunately the beginning of the National Health Service and the advent of chemotherapy occurred at almost the same time and in Newcastle the University Department of Child Health had been established in 1942. The work of the chest physicians at the two chest clinics was later related to the hospitals where their patients were treated and came into the hospital service. But the home visiting of contacts and others remained a function of the local health authority. There was also great interest regarding tuberculosis in children in the university department, members of which were on the staff of all the children's hospitals and units in the city, the maternity hospitals and, after 1947, the children's sanatorium. The possibility of BCG vaccination for non-infected contacts and the extension of vaccination to school leavers were also matters of importance requiring detailed organisation and recording.

In 1952 therefore the children's contact service was made a separate section of the city health department and a children's tuberculosis officer (MDT) appointed. She had had special experience of paediatrics and tuberculosis in children and worked closely with the physicians at the chest clinics, the paediatricians in the children's hospitals, and later with the staff of the school health service. The work was described in detail in 1963 but must be indicated here.[3] It was associated with the children's services of the city in hospitals or child health clinics. There were contact clinics for children under 5 years. Older children had a special clinic on a Saturday morning or after school hours. All children admitted to any hospital were given a tuberculin test, those positive were investigated further, and a register of tuberculin positive children was compiled from all sources. From 1954 school leavers were tuberculin tested and those negative were offered BCG; at first this operated only in maintained schools but after 1958 in all schools within the city. All the testing was done by members of the school health service.

From 1955 a tuberculin test became part of the routine school medical inspection of 10 year old children and in 1956 the test was offered to children in their first school year. All children found positive and their families were investigated. In that way we were able to supervise tuberculin positive children and at the same time observe the decline in the numbers of children positive at the various ages. After the

Table 8 Newcastle upon Tyne 1973–88 (inclusive). Tuberculosis deaths at all ages (years)

	<15	*15–24*	*25–34*	*35–44*	*45–54*	*55–65*	*>65*	*Total*
1973–79	0	1	0	1	13	21	43	79
1980–88	0	0	2	3	2	13	39	62

introduction of isoniazid it was possible to treat primary infection without injections and without admission to hospital, and after 1953 we treated all tuberculin positive children under 5 years of age, and since 1960 no Newcastle child has died from tuberculosis.

Our story concerning Newcastle children and tuberculosis is ended. New notifications of adult tuberculosis are now very few but the contact work and BCG vaccination continue. In 1972, 12 deaths of adults were recorded (table 2) and, in table 8 the deaths from 1973 to 1988 have been brought together in two groups divided into age groups. The striking and welcome fact is that no child died and only one person under 25 years. More than half the deaths were in people age 65 years or more; two thirds were men. A more detailed study was not possible but the figures suggest that these deaths are the result of the breakdown of old lesions or respiratory failure associated with fibrotic or other changes.

Thus the decline from the beginning to the mid-point of this century was succeeded by the fall over the next 25 years and deaths from tuberculosis are disappearing from our society—but we need to keep our defences for another generation and protect everyone from natural primary infection.

Throughout this paper use has been made of the reports of the medical officers of health of Newcastle from 1874–1972 held in the Robinson Library, the University of Newcastle upon Tyne.

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Dr Florence Siebert (1897–1991): she gave us PPD

It is given to few people to know that they have given to the world something of immense value but such a person must have been Dr Florence Siebert who died in Florida on 23 August 1991 at the age of 93 (Obituary in *The Times* on 3 September 1991).

She was born in Eaton, Pennsylvania, in 1897. At the age of 3 she contracted polio and thereafter needed to wear leg calipers. She took a PhD in chemistry at Yale but it was as a Guggenheim fellow at the University of Uppsala in Sweden that she isolated purified protein derivative (PPD) in 1934 and in 1941 a single large batch was deposited as an international standard. Thus tuberculin testing was standardised for the first time. Robert Koch had produced crude tuberculin from a boiled culture of tubercle bacilli in 1880[1] but had proposed it as of therapeutic rather than diagnostic use. Dr Charles Mantoux (1877–1947) of Cannes described the intradermal tuberculin test in 1908[2] but, interestingly, the idea of using tuberculin as a diagnostic agent has been attributed to Sir Arthur Conan Doyle.[3]

Florence Siebert is a name previously unsung in my ears but in future whenever I ask for a tuberculin test I shall think of her.

ARCHIVIST

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Archives of Disease in Childhood 1992; 67: 256

LETTERS TO THE EDITOR

Radiological reliability in atlantoaxial subluxation

Sir,—I read with great interest the thought provoking article by Selby and associates.[1] The authors have found atlantoaxial subluxation in 18 out of 131 patients with Down's syndrome. Repeat radiographs performed at 10 minute intervals in 19 patients, including six with subluxation, showed that in three patients the abnormality was not seen in both sets of radiographs. They attribute the lack of radiological reliability to the changes in the muscle tone and ligamentous laxity. However, they fail to mention the position in which the radiographs were taken.

The horizontal ray lateral view taken with the patient in the supine position reveals the full extent of any abnormal slippage due to laxity of the transverse ligament as the weight of the neck muscles will force the odontoid process to separate from the anterior arch of atlas and serves as a dynamic test of integrity of the atlantoaxial joint, whereas, if the patient is examined erect or prone, the gap narrows.[2]

The other possible explanation for variability in the values could be due to improper technique of obtaining flexion and extension views. At the end of flexion movement, when the chin abuts against the sternum, some deflexion occurs at the level of cervico-occipital junction. The maximal flexion of the upper cervical segment is obtained only by drawing the head as far back as possible and then tucking the chin in. Correct extension of the upper cervical region is obtained by drawing the head forwards as far as possible and then extending without moving the neck backward.[3]

The odontoid peg has three ossification centres[4] and not four centres as mentioned by the authors.

Computed tomograms of the craniovertebral junction should be done before rejecting radiographs of the neck as unreliable at identifying atlantoaxial subluxation.

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Dr Selby comments:

I would like to make the following points in reply to the letter from Dr Prakash. Firstly, it is mentioned both in the text and in table 4 that the radiographs were taken in flexed, extended, and neutral positions in both the initial and in the repeated films. Secondly, I accept that correct positioning is important in radiological diagnosis of atlantoaxial subluxation and care was taken by experienced paediatric radiographers in the accurate positioning of the children. Information on odontoid hypoplasia can be seen in papers by McManners[1] and Elliot *et al*.[2]

Finally, the reason for our paper is that at present the recommendations of the Department of Health[3] and the American Academy of Pediatrics is that a child with Down's syndrome may or may not be eligible to partake in active sports dependent on the normality of plain radiographs of their cervical spine. We do not feel that these are valid recommendations.

I would agree that a child with neurological abnormality would need further investigation and subsequent intervention and stabilisation. I do not know of any study which has looked at a large number of children with Down's syndrome for atlantoaxial subluxation with tomography.

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Abdominal pain in Henoch-Schönlein purpura

Sir,—We read with interest the report by Hu *et al* on the use of ultrasonography to diagnose and exclude intussusception in children with Henoch-Schönlein purpura.[1] We agree with the authors that ultrasound is an excellent, non-invasive procedure to assess for the presence of intussusception. We also agree that the incidence of intussusception in children with Henoch-Schönlein purpura is likely higher than reported.

We believe that the history and physical examination are the best ways to differentiate whether an intussusception is present. Our experience suggests that there are several kinds of abdominal pain in children with Henoch-Schönlein purpura. The most common abdominal pain is a dull, constant, periumbilical pain which is due to inflammation and bleeding in the intestinal wall and results from the underlying vasculitic process. This pain is not colicky and there are no peritoneal signs by abdominal examination. The abdominal pain associated with intussusception is characteristically colicky and intermittent. The stool may contain blood and mucous ('red current jelly' stool). Other symptoms and signs of intestinal obstruction such as vomiting, abdominal distension, and increased bowel sounds may be present. An abdominal mass may be palpable, and there may be a feeling of emptiness in the right iliac fossa. Peritoneal signs are absent. This intermittent colicky pain is usually superimposed against the background of the more common dull and constant periumbilical pain. If an intestinal perforation occurs, the abdominal pain is constant, generalised, and peritoneal signs such as abdominal wall rigidity and infrequent bowel sounds are evident by physical examination. Ureteritis has been reported in Henoch-Schönlein purpura and may also present with colicky pain.[2] This colicky pain may be distinguished from that due to intussusception by its location in the flank or the groin.

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Multiple admissions under 2 years of age

Sir,—I read with interest the article by Spencer and Lewis and was extremely impressed by the figures they present as far as total admissions are concerned.[1]

We have undertaken some research in Portugal in all the paediatric departments of the country (85 hospitals). The results for years 1989 and 1990 are shown in the table.

Hospital admissions in 1989 and 1990

	1989	*1990*
Total births	118 560	116 383
Total children aged (years):		
1–4	500 000	487 000
5–9	740 000	731 000
Children admitted to hospital aged (years)*:		
0–1	13 019	12 443
1–4	15 179	14 503
5–9	10 923	10 856

*The study included paediatric departments only. Paediatric surgery, and surgery for ear, nose, and throat and orthopaedics, and other 'adult' departments were not included.

Our study aimed to gain some information about acute respiratory infections and we found that 24·96% of all admissions were caused by these infections. The figures were similar for central and district hospitals. In a one day study performed in 1990 in child health clinics of three districts of Portugal we found that 8·4% of children aged less than 2 years of age, who were attending the health centre on that day, had been admitted to hospital during the previous six months.

The psychological, emotional, physical, social, and economic consequences for the child, the family, and the admitting institution that is caused by admission have been fully described and are undoubtedly a major problem in social paediatrics. The article by Spencer and Lewis is an excellent contribution to this challenge.

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Annotations

The urgency of immersions

Accidental child drowning continues to challenge many specialty disciplines in the broader field of child health. Despite resolute community based attacks on the problem of immersion accidents,[1–4] some now going back more than 15 years,[5 6] resuscitators, intensive care physicians, and paediatricians remain frequently involved. Epidemiologists, preventive medicine exponents, and legislators have had some success in reducing the numbers of fatal immersion incidents in childhood.[4 7] Much remains to be done.

Clinical approaches to the management of the near drowned child have seen big changes in the past decade.[8] The management pendulum has swung from that of basic life support in the late 1970s, through a phase best described as an aggressive but empirical interventionist approach,[9] back to a current intermediate position of advanced life support[10 11] for the child after immersion with a minimum of a residual heart beat. The years of the 1980s were controversial, not necessarily a bad thing in itself, but were wanting in the publication of sufficient control studies to lift treatment of the near drowned from the empirical to rational objectivity. Such studies are still awaited.

Epidemiological approaches to prevention have also been controversial, certainly at the community level of society. In the suburbs and on the farm, in a few enlightened societies, the reduction of the threat to children from water hazards has been bought at the expense of personal freedom, and considerable financial expense. In those countries (for example, Australia and New Zealand) that have grappled to introduce safety legislation for water hazards, and those countries in which it has been advocated, there has been bitter and prolonged public debate not only about the potential efficacy of such legislation but also its fundamental philosophy.

Epidemiology

The risks of drowning vary obviously with the density of water hazards in any child's environment. Children living in water oriented societies, especially those with major recreational use of the sea, lakes, rivers, and swimming pools are at special risk. In the USA more than 2000 children drown each year,[12] and residual neurological deficits occur in a percentage of another 8000 survivors.[13] In the UK drowning has caused an average of 72 child deaths per year for the past 10 years.[14] Another 150 cases per year survive, some 5% of whom have significant neurological abnormalities. There are particular problems in New Zealand.[2] Some 800 toddlers have drowned in home swimming pools in Australia since the epidemic threat to children was first recognised,[5 6] and more than 1000 survivors have been pulled pulseless from the water. Some 30% of survivors from fresh water near drowning manifest measurable residual deficits,[15 16] a minimum of 3% existing in a permanent vegetative state.[4 15]

Accident syndromes

There are several distinct drowning 'syndromes' in childhood: bath tubs,[17 18] pools and ponds,[2–5 8] rivers and lakes,[5 8] and sea,[7 19] vehicle immersions with child occupants,[20] spa pools,[21] child abuse and homicide by immersion,[8 22 23] and alcohol related water accidents involving older teenagers.[8 24 25] All have different peak ages of risk, and all require different and highly specific approaches to primary prevention.[5 8]

Clinical management

From the clinical point of view, skilled rescue site resuscitation will convert some 30% of (otherwise) fatalities into survivors. If any suspicion of hypothermia[8 16] or drug ingestion[8 25] exists, resuscitation should be continued until mechanical ventilation can be instituted, and these potential confounding variables clarified. Mechanical ventilation and positive end expiratory pressure,[8 11] and probable monitoring of intracranial pressure, remain the mainstay of treatment. One of the 'holy grails' of the resuscitation world is the search for a brain sparing drug to be given after the event. After the disappointment of the attempts using barbiturate rescue, there is nevertheless some hope that other drugs will hold promise. Appropriately controlled animal studies with blinded operators and observers are needed before further clinical trials are undertaken. Outcome predictors (once the child has reached the intensive care ward) such as persistent hypoxaemia, persistent acidosis (pH below 7·0),[8] the 'time to the first spontaneous gasp,[8] and the use of the Glasgow coma scale[11] all enable reasonable predictions of significant neurological damage to be made. Provided hypothermia is not a feature of a near drowning episode, children who do not make their first spontaneous gasp within 40 minutes or so after extraction from the water, and in whom skilled resuscitation is being performed, virtually never escape serious neurological damage. Skilled and standard intensive care techniques are such that it is unlikely that a child with an intact heartbeat will die subsequently. Salvage rates, at least in terms of a child with a beating heart and spontaneous intact respiration, exceed 80% of those cases who arrive alive in the intensive care unit. All the studies of childhood freshwater pond and pool immersions have found a minimum of a 50% survival rate, and although better resuscitation is condemned by some as only 'secondary prevention', it offers a potential short term solution to saving many children's lives.

The biggest challenge to clinical management therefore is improving prehospital resuscitation. Questions about the efficacy of out of hospital resuscitation are controversial and topical,[26 27] but our experience with child near drowning victims leads us to the uncompromising viewpoint that 'every parent should be a first aider'. Attempts to institute such a policy, at least for pool owning families, have so far failed. However, by continued societal advocacy, paediatricians can create a public ambience where such must come to be regarded as one of the essential skills of parenting. May that time roll on.

Prevention and a medical model

The biggest impediment to the solution of childhood immersions is the failure of the medical profession to adopt a medical model to deal with the problem. Despite the fact that immersion continues to rank as one of the major killers of young children in many parts of the world, many remain reluctant to accept this as a medical or public health problem. The techniques of preventive medicine are well honed in the area of infectious and nutritional disease as these occur in the childhood years. Genetic diseases are currently vigorously approached by the portals of genetic counselling and prenatal diagnosis. Child trauma more generally has responded to aggressive intervention using the traditional themes of preventive medicine, but drowning remains the poor relation when judged by any audit of results revealed in contemporary surveys. One reason for this is the very high fatality:survivor ratios for immersion accidents. For every child who drowns, another (1:1) is pulled from the water pulseless but who subsequently responds to resuscitation. In the case of road trauma the ratio is 1:20 and 1:2000 in the case of accidental poison ingestion. Thus the size of the problem is partly masked as most of the immersion victims bypass the hospital and go straight to the mortuary, and are not seen in the ambience of the intensive care wards. Furthermore, in many countries society at large has been conditioned by newspaper reports of yet 'another toddler drowning fatality'. It is thus by continued advocacy, and the use of traditional methods that have conquered other high ranking problems in preventive medicine, that this problem will be effectively addressed. Currently the urgency of childhood immersions is the responsibility of us all.

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Reactive amyloidosis

Reactive amyloidosis (also known as systemic amyloidosis or secondary amyloidosis) is a disorder which occurs as a complication of chronic inflammatory disorders such as juvenile chronic arthritis, chronic infective disorders such as bronchiectasis, osteomyelitis, tuberculosis, or leprosy in susceptible individuals. It is also responsible for renal failure in the hereditary form of amyloidosis associated with familial Mediterranean fever, particularly in North African Sephardic Jews.[1] Recently it has been described to have been the cause of the severe and rapidly fatal nephropathy which occurs in adolescents with cystic fibrosis.[2] The table is a summary of the different types of amyloidosis.

Fibrillar proteins are deposited together with glycosaminoglycans (GAG), serum amyloid P component, and fibrinectin, leading to cellular dysfunction. The spleen appears always to be involved in reactive amyloidosis. The kidneys, liver, adrenal gland, and gastrointestinal tract are frequently involved. By light microscopy, the amyloid deposit appears as a homogeneous eosinophilic material that stains with Congo red. Under polarised light microscopy the congophilic material has a characteristic apple green birefringence.

Pathogenesis of reactive amyloidosis

The protein that forms the fibrils in amyloid deposits is

Amyloidosis syndromes

Distribution of deposits	*Clinical type*	*Chemical type*	*Fibril proteins and precursors*
Systemic amyloidosis	Associated with immunocyte dyscrasia	AL	γ or ϰ light chains derived from monoclonal immunoglobulin light chains
	Associated with chronic inflammatory diseases	AA	Amyloid A derived from serum amyloid A protein
	Associated with chronic haemodialysis	AH	β_2-Microglobulin
	Senile systemic amyloidosis	ASc	Prealbumin-like, derived from plasma prealbumin
	Hereditary syndromes: Predominantly neuropathic forms (all autosomal dominant): Types I–IV	AFp	Mainly prealbumin variants
	Predominantly nephropathic forms: Associated with familial fever (autosomal recessive)	AA	Amyloid A derived from serum amyloid A
	Ostertage type (autosomal dominant)		Not known
	Muckle-Wells type (nephropathy with deafness, urticaria, limb pain)		Not known
	Predominantly cardiomyopathic forms:	AFc	Prealbumin variants
Localised amyloidosis	Senile amyloidosis (heart, joints, seminal vesicles)		Atrial, natriuretic, peptide related fibrils in isolated atrial amyloid
	Cerebral amyloid angiopathy and cortical plaques in Alzheimer's disease, senile dementia and Down's syndrome		B-Protein, precursor encoded on chromosome 21
	Endocrine amyloidosis: Medullary carcinoma of thyroid insulinoma and type II diabetes	AE AEt	Precalcitonin-like protein calcitonin related, peptide like protein in pancreas
	Isolated massive nodular deposits (skin, lung, urogenital tract)	AL	Monoclonal immunoglobulin light chains
	Primary localised cutaneous amyloid (macular, papular)		? Keratin derived.
	Ocular deposits (corneal, conjunctival)		Not known
	Hereditary syndromes: Hereditary cerebral haemorrhage with amyloidosis (Icelandic type) (Dutch type)	AFb	Cystatin C (γ trace), Glu58 genetic variant of cystatin C β-protein

derived from a serum acute phase protein, serum amyloid A. The carboxy terminal end of serum amyloid A is cleaved off leaving the first 76 amino acids, which then form polymers resulting in β-pleated sheets of fibrils embedded in GAG, serum amyloid P, and possibly other extracellular matrix proteins. The local appearance of GAG appears to be coincident with the time that the fibrillar proteins are deposited in experimentally induced amyloidosis in mice. Furthermore, if the substance amyloid enhancing factor (AEF) is injected at the same time as the inflammatory stimulus, then amyloid deposition is accelerated. AEF is ill defined at the present, but has a protein component which is neither serum amyloid A nor serum amyloid P. The substance was originally isolated from amyloid deposits. In reactive amyloidosis, it appears that circulating serum amyloid A or locally produced serum amyloid A are not degraded fast enough within the extracellular microenvironment and the result is an accumulation of this degradation product of serum amyloid A. Analysis of the rate of degradation of serum amyloid A in the presence of macrophage or neutrophils has not shown any differences between patients with amyloidosis and those without. In the extracellular microenvironment, however, the cells may have different characteristics than circulating monocytes and neutrophils. Therefore it is still possible that the degradation enzyme(s) for serum amyloid A may not be produced fast enough or be deficient. The ability to clear amyloid protein breakdown products may be genetically determined.

Variation in the degradation rate of amyloid fibres could also be due to other proteins produced locally which inhibit efficient degradation by available enzymes. Hypersecretion of either serum amyloid P or GAG in the proximity of serum amyloid A proteins may inhibit their breakdown. It is interesting that we have previously shown that serum amyloid P can be a marker in amyloidosis associated with juvenile chronic arthritis.[3] The marker is not related to differences in the structure of serum amyloid P protein, but it is likely that this marker is associated with the promoter region of the serum amyloid P gene and therefore would influence the level of secretion of serum amyloid P. This work is currently under study.

In summary, the clearance of serum amyloid A protein and its breakdown products is a crucial element in the development of amyloidosis and may be genetically determined. This hypothesis would explain the findings in our patients with juvenile chronic arthritis as described below, where only a small percentage of patients with identical illness have developed amyloidosis, and the regression rate is highly variable.

Amyloidosis in juvenile arthritis

PREVALENCE

The prevalence of reactive amyloidosis varies between 1–10%. The British (7·4%) and German (3·1%) reports have higher prevalence compared with the American (1·8%) centres.[4–6] The reason for this is not entirely clear. It may be due to selection bias of various centres, length of follow up, possible differences in genetic background, and perhaps a tendency for more aggressive treatment early on in the disease in the USA. In Poland, where there is a more thorough reporting of cases of juvenile arthritis to a central board, the prevalence of amyloidosis is highest at 10·6%.[7]

The prevalence of amyloidosis is highest in systemic onset juvenile chronic arthritis compared with the other subgroups of juvenile arthritis. In the German series 92% of the patients were of systemic onset.[5] Our own data show that although amyloidosis is more frequently a complication of systemic juvenile chronic arthritis, polyarticular disease contributes 26% to the amyloidosis in our follow up group.[8]

The prevalence of amyloidosis is similar in adult rheumatoid arthritis.[9] In contrast, the prevalence in other inflammatory diseases like systemic lupus erythematosus and inflammatory bowel disease are much lower.[10]

CLINICAL FEATURES

Amyloidosis is usually suspected when proteinuria occurs. In the initial stages the proteinuria may be intermittent. The patient is unwell, out of proportion to his/her inflammatory disease. Hypertension usually occurs later as a result of decreasing renal function. Abdominal discomfort due to oedema of the bowel may occur. Splenomegaly is found in about 60% of patients; however, the spleen is involved in all patients shown to have reactive amyloidosis by scanning techniques or at postmortem examination.[11]

LABORATORY FEATURES

There is invariably evidence of a raised acute phase response, that is, anaemia, raised erythrocyte sedimentation rate and C reactive protein, hypergammaglobulinaemia, and reduced albumin. Interestingly, immunoglobulin deficiency may also be seen in amyloid patients. In the Polish series there were 33 amyloidosis patients with immunoglobulin deficiency, particularly IgA and IgG, and these patients have the highest mortality.[12] Treatment with chlorambucil may contribute to hypogammaglobulinaemia and overwhelming infection may occur in these patients. A small amount of immunoglobulins may be lost due to urinary loss.

METHODS OF DIAGNOSIS

The definitive diagnosis of amyloidosis has, until very recently, relied upon the histological findings of congophilia on tissue biopsy specimens. The main source of tissue was rectal biopsy. More pleasant and reliable sites to biopsy include subcutaneous fat and the gums. Renal biopsy may be hazardous and the incidence of perinephric haematoma is not insignificant. There were three such cases in our series of 25 renal biopsies for amyloidosis. The cause of the excessive bleeding is due to the amyloid infiltration of the submucosa of blood vessels and thus reducing their contractability. Furthermore, a number of workers have demonstrated a prolonged bleeding time in these patients.[13] Bleeding diathesis may further occur as a result of reduced hepatic synthesis of clotting factors, although these have not been systemically measured.

In 1988 Hawkins *et al* described a new non-invasive isotope method of diagnosing amyloidosis.[14] The basis of this investigation relies on the high affinity of serum amyloid P for all types of amyloid fibril. In patients with amyloidosis when radioiodinated isologous serum amyloid P is given intravenously it rapidly leaves the vascular compartment and localises within the amyloid deposits, that is, a rapid plasma clearance of serum amyloid P is seen in amyloidosis. The distribution of labelled amyloid deposits is demonstrated by scintigraphy by the gamma camera, usually performed after 24 hours. The whole body retention of radioactivity is increased and this is measured indirectly as an inverse of the urinary isotope excretion over a seven day period. This technique has become essential in our investigation of the juvenile chronic arthritic in whom a diagnosis of amyloidosis is suspected. It has been useful in diagnosis, monitoring the response to treatment, and in revealing unsuspected organ deposits, particularly adrenal infiltration. This infiltration is important to recognise as it may be responsible for the collapse seen in amyloidosis sufferers with infection.

TREATMENT OF AMYLOIDOSIS

Colchicine is known to prevent and ameliorate the progression of amyloidosis in sufferers of familial Mediterranean fever before the onset of nephrotic syndrome.[1] With established nephrotic syndrome, colchicine is no longer effective. Dimethylsulphoxide (DMSO) has been extensively evaluated. It has been suggested that it may be effective in dissolving subunit proteins.[15] Most experience, however, suggests that it is ineffective and furthermore, extremely unpleasant owing to the odour which is released after ingestion/topical application.

To date, the most effective method of management is by cytotoxic treatment. The aim is to completely repress the acute phase response and thereby reduce the raised concentrations of serum amyloid A. Ansell began using chlorambucil for the treatment of amyloidosis complicating juvenile chronic arthritis in the early 1960s. In the report of Schnitzer and Ansell it was seen that disease activity was controlled within one to three years of treatment.[4] Of all patients who had proteinuria at onset 64% had no proteinuria after three years or more. Berglund *et al* reported an improvement in survival in 14 patients with rheumatic diseases and renal amyloidosis with alkalating agents in particular chloramubucil.[16] Ahlem *et al* found a five year survival rate, which improved from 27% in untreated controls to almost 90% in 22 patients who took part in a randomised prospective trial of treatment with variety of cytotoxic agents.[17]

Our own data confirm the improved survival in those treated with chlorambucil. At our 15 year follow up, 68% of chlorambucil treated patients with juvenile chronic arthritis and amyloidosis were alive in contrast to no patient in a non-cytotoxic treated group. Chlorambucil is used at a dose of 0·1–0·12 mg/kg/day. It is given as a single oral dose and well tolerated by the patient. Bone marrow toxicity may occur and needs to be monitored. It is usually reversable and rarely requires cessation of treatment. In our series of 79 patients, there was only one (1·75% incidence) who developed acute myelomonocytic leukaemia. This particular patient had previously received 3 g of azathioprine, which may contribute to the overall oncogenic effect, and died with advanced renal failure.

With the much improved survival figures, fertility status of the patient has been a clinical problem. No male patient in our series fathered a child. This infertility in male patients is further supported by other series.[18] In our female population premature ovarian failure occurred in six women. There were, however, three women who had uncomplicated and successful pregnancies.

CAUSE OF DEATH

The vast majority of patients with juvenile chronic arthritis that was complicated by amyloidosis died with renal failure (84%). Patients are at risk of developing acute renal failure even when the amyloidosis is controlled because of the impaired renal function. Twenty five percent had renal fibrosis and hypertension. Acute tubular necrosis has been described.[19] Infection is the second commonest cause of death, usually due to bacterial septicaemia. Immunosuppression and adrenal insufficiency are contributory. The nephrotic syndrome itself may be immunocompromising due to the urinary loss of immunoglobulin.

REGRESSION OF AMYLOIDOSIS

There have been case reports of regression of amyloidosis from repeat renal biopsy and postmortem studies. In experimentally induced amyloidosis in mice, amyloid deposits regress and disappear after cessation of the stimulus. With the advantage of the serum amyloid P scan method, we were able to demonstrate the absence of amyloid deposits in four individuals in remission of their juvenile chronic arthritis, all having previous histological evidence of amyloidosis. In addition, one patient who was scan positive became scan negative one year after remission. The rate of regression is highly variable, however, and this is currently the subject of further studies.

Conclusions

Despite the progress in the understanding of the pathogenesis of amyloidosis and also the diagnostic field, many questions remain unanswered. The most important clinical question is that of a safe and effective drug for the control of amyloidosis. To date, chlorambucil remains the single agent which has been used to improve survival significantly. Scanning with serum amyloid P labelled with I^{123} has facilitated non-invasive evaluation of a potentially life threatening complication of juvenile chronic arthritis.

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ORIGINAL ARTICLES

Congenital retinal dystrophies: a study of early cognitive and visual development

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Abstract

The reported incidence of mental retardation in Leber's congenital amaurosis has varied from 10% to 87%. There has been no review of the estimate since it became possible to delineate an increasing number of diagnostic subcategories. In this study, the visual and cognitive development of 38 children with congenital retinal dystrophies has been followed up prospectively. Children with associated disorders in other systems and those with central nervous system malformations or degenerations were significantly more likely to have learning disability than those without additional medical problems. Most subgroups made little or no visual progress with the exception of the group with associated hypoplasia of the cerebellar vermis. The study highlights the importance of using the specialised techniques now available to delineate fully the visual diagnosis and paediatric perspective because of their relevance to congitive and visual prognosis.

The congenital retinal dystrophies (CRDs) are a group of rare disorders in which severe visual impairment from early infancy results from dysfunction of retinal receptors. The electroretinogram is characteristically absent or severely attenuated; visual evoked responses are usually reduced. The appearance of the retina is normal or near normal in early childhood, differentiating these conditions from the retinal dysplasias, although degenerative or pigmentary changes may occur later. All these dystrophies are hereditary, most being autosomal recessive.

The first of these conditions to be described, in 1869, was Leber's congenital amaurosis,[1] and until recently this has remained the 'umbrella' diagnosis given to patients with CRD. However, with increasing recognition of the heterogeneity of these disorders,[2–4] several genetically distinct subtypes of Leber's amaurosis and an infantile onset form of retinitis pigmentosa have been delineated.[2–6] It has also been recognised that retinal dystrophy can be associated with brain malformation as in Joubert's syndrome[7] or may be a presenting feature of neurodegenerative disorders such as Zellweger's disease.[2 8 9] Precise diagnosis can still be difficult at presentation, and an initial label of Leber's amaurosis may need revision.[2]

This heterogeneity makes it difficult to interpret previous reports of the incidence of severe learning disability in Leber's amaurosis which vary from 10% to 87%.[3 4 10 11] It is possible that some of the retarded children described in these studies would today be more precisely categorised.

The present study was undertaken to examine cognitive and visual progress in the first five years of life in the congenital retinal dystrophies, within and between diagnostic subgroups.

Methods

SUBJECTS

Four hundred severely visually impaired children attended the Developmental Vision Clinic at the Wolfson Centre between 1972 and 1989. Forty two fulfilled the definition of congenital retinal dystrophy described in the introduction and were aged less than 5 years when first seen. Four aged less than 12 months at last assessment were excluded because judgments on verbal development would have been inappropriate. The remaining 38 children form the study population.

All the children had full ophthalmological examination and investigation, including electrophysiological studies, in the department of ophthalmology at the Hospital for Sick Children, Great Ormond Street. Other investigations, including computed tomography brain scans and metabolic studies, were performed where appropriate in the departments of neurology and metabolic diseases. An umbrella diagnosis of Leber's amaurosis given earlier was refined in eight children as a result of follow up investigations. Revised diagnoses were used in this study.

The 38 children were allocated to four groups according to the nature of the retinal dystrophy and the presence and nature of other medical problems or disabilities (table 1). The children in groups III and IV all had central nervous system malformation or degeneration. Groups I (Leber's congenital amaurosis) and II ('other' congenital retinal dystrophies) were subdivided into those with and without additional chronic medical problems or disabilities. As the aim of the study was to explore development within

Table 1 Distribution according to diagnostic category

Diagnostic category		*No of children*
I	Leber's congenital amaurosis Ia No medical problems (n=13) Ib With medical problems (n=7)	20
II	'Other' congenital retinal dystrophies IIa No medical problems (n=3) IIb With medical problems (n=3)	6
III	CRD with cerebellar vermis hypoplasia	7
IV	CRD with neurodegenerative disorder	5
Total		38

CRD, congenital retinal dystrophy.

and between diagnostic categories, the level of intellectual function was not taken into account in allocation. Groups II, III, and IV all contained children in whom an initial label of Leber's amaurosis had been revised.

None of the 13 children with Leber's amaurosis in group Ia had any additional medical or sensory problems. The seven children in group Ib had well recognised associations of Leber's amaurosis: three had sensorineural deafness, two had impaired renal concentrating ability, one had small renal cysts (renal function was otherwise normal in all three), and one had cardiomyopathy.

The visual diagnosis in the three children without additional medical problems in group IIa was congenital cone dysfunction. In group IIb the additional medical problem was epilepsy in one child with congenital stationary night blindness, deafness in one of the two children with infantile onset retinitis pigmentosa, and hypotonia with motor delay in the other.

Five of the seven group III children with cerebellar vermis hypoplasia had presented with the abnormal breathing patterns in infancy of classical Joubert's syndrome. All seven had motor disability with hypotonia and ataxia, six had saccade palsy, and one developed renal failure due to nephronophthisis at the age of 5 years.

The diagnosis in two of the five children in group IV in whom CRD was part of a neurodegenerative disorder was Zellweger's syndrome. A specific diagnosis was not possible in the other three despite extensive investigation. All had multiple additional disabilities. Motor disability presented as hypotonia in four children and choreoathetosis in one. The two with Zellweger's syndrome were also deaf and had abnormal liver function. One of the others was deaf and progressive cerebellar atrophy was documented in another.

Only four children had experienced adverse perinatal events: two were premature, one in group Ib and one in group III; one in group III had duodenal atresia and one in group IIb had hyperbilirubinaemia requiring exchange transfusion.

PROCEDURES

Children are seen at each visit to the clinic by a developmental paediatrician, psychologist, and specialist health visitor experienced in the assessment and management of babies and young children with severe visual disability. A speech therapist, occupational therapist, and physiotherapist are involved as appropriate. Assessment findings are developed into programmes to promote many aspects of cognitive and motor skill and visual development.[12–14] Babies are reassessed and their programmes updated every four months during the first year, every six months during the second, and annually thereafter. Development is monitored at each visit by the psychologist or developmental paediatrician on the Reynell–Zinkin scales for young visually handicapped children.[15] These scales provide an age level of function rather than a quotient, with standards for blind, partially sighted, and sighted children. The distinction between blind/very severely visually impaired (VSVI), and partially sighted/moderately severely visually impaired (MSVI) was made according to criteria given below.

Progress was monitored on the three most intellectually loaded subscales: response to sound and verbal comprehension, expressive language (structure), and sensorimotor understanding. The standard appropriate to a child's degree of visual impairment was used to designate development as normal or delayed. Children falling on or above the standard were designated normal and those falling below as delayed for that scale of development.

Vision was assessed at each visit by a method appropriate to the child's developmental stage; either a series of solid round objects graded in size from a 12·5 cm ball to 1 mm cake decoration known as 'hundreds and thousands'; or standard Snellen optotypes. All the children were severely visually impaired. The degree of visual impairment was classified as very severe (VSVI) if a child was unable to see a 2·5 cm cube at 30 cm or had a best corrected acuity of less than 1/60; and as moderately severe (MSVI) at levels better than this.

The degree of visual impairment was very severe in nine of the 13 with uncomplicated Leber's amaurosis (group Ia); in five of the seven children with Leber's amaurosis and other medical problems (group Ib); in none of the three children with cone dystrophy (group IIa); in one of the three with 'other' CRDs and medical problems (group IIb); in three of the seven with cerebellar vermis hypoplasia (group III); and in four of the five children with neurodegenerative disorders (group IV).

Results

There was no significant difference between diagnostic groups in age at first attendance or length of follow up. The sexes were evenly distributed except in group II, where five of the six were boys.

COGNITIVE PROGRESS

Table 2 summaries the results for cognitive development within each diagnostic subgroup. Twenty three (61%) of the children were developmentally delayed on one or more of the Reynell–Zinkin subscales. The distribution and pattern within each diagnostic group is first described.

Group Ia

Ten children (77%) performed at or above the relevant standard in all three subscales of the Reynell–Zinkin scales. Three (23%) were delayed in one or more fields; one in all three fields (see table 3); one in sensorimotor understanding; and one in expressive language. There was no difference between the non-delayed and delayed patients according to sex distribution (5/10 and 2/3 boys) or degree of visual impairment (7/10 and 2/3 VSVI). The incidence of developmental delay in this group is similar to that found in severely visually impaired children whatever the cause.[10 12 16]

Group Ib

Only one child in this subgroup, the child with renal cysts, performed above the relevant standard in all three fields of development. The remaining six (86%) were delayed, five in all fields and one in expressive language and sensorimotor understanding.

Group IIa

All three children with congenital cone dysfunction progressed normally in all three fields of development.

Group IIb

The child with infantile retinitis pigmentosa and motor delay made normal intellectual progress; the other two children were delayed in all three fields.

Group III

All seven children were delayed in at least one field. Three were severely globally retarded and the other four all had severe oral dyspraxia with severe delay in expressive language. Three of the latter were moderately delayed in other fields though one achieved normal scores in sensorimotor understanding and verbal comprehension.

Table 2 Developmental progress by diagnostic category. Results are number (%)

Diagnostic category		No delay	Delay
Ia	Leber's—no other problems	10 (77)	3 (23)
Ib	Leber's—with other problems	1 (14)	6 (86)
IIa	'Other' CRDs—no other problems	3 (100)	0 (0)
IIb	'Other' CRDs—with other problems	1 (33)	2 (67)
III	CRD with cerebellar vermis hypoplasia	0 (0)	7 (100)
IV	CRD with neurodegenerative disorder	0 (0)	5 (100)

CRD, congenital retinal dystrophy.

Table 3 Clinical details of four children showing deceleration or regression of development

Medical perspective	Developmental and behavioural changes	Other factors
Uncomplicated Leber's amaurosis (Ia)	Deceleration and behavioural changes with 'autistic' features in second year	—
Leber's amaurosis with impaired renal concentration (Ib)	Deceleration and behavioural changes with 'autistic' features in second year; regression in third year; unexpected death age 3·5 years	Family prolems during second year
Leber's amaurosis with impaired renal concentration (Ib)	Deceleration and disorder of language development in third year	—
Congenital stationary night blindness (IIb)	Deceleration in third year. Epilepsy+attention deficit disorder in fourth year	Neonatal jaundice

Table 4 Visual progress by diagnostic category

Diagnostic group	Visual function			Final visual level	
	No change	Better	Worse	VSVI	MSVI
I Leber's amaurosis	19	0	1	14	6
II 'Other' CRDs	6	0	0	1	5
III CRD with cerebellar vermis hypoplasia	2	5	0	1	6
IV CRD with neurodegenerative disorders	4	1	0	3	2

CRD, congenital retinal dystrophy; VSVI, MSVI, very severe and moderately severe visual impairment.

Group IV

All five children were severaly globally retarded.

Clear differences in the distribution of learning disability were seen between diagnostic categories; their significance was determined using the Fisher exact probability test. Children without chronic medical problems or sensory or motor disability (groups Ia and IIa) were significantly less likely to be delayed than those with such problems (group Ib, IIb, III, and IV): 3/16 and 20/22 respectively ($p<0{\cdot}001$). The difference remained significant when those with documented central nervous system malformation or degeneration (groups III and IV) were excluded: 3/16 children in groups Ia and IIa were delayed compared with 8/10 in groups Ib and IIb ($p<0{\cdot}01$). Even within the group with Leber's amaurosis the difference between those with and those without other medical problems reached significance: 6/7 children in group Ib were delayed compared with 3/13 in group Ia ($p<0{\cdot}025$).

Four of the 38 children showed slowing or regression of development during the first 12 to 18 months. The slowing was accompanied by the appearance of some autistic features in two children. Clinical information is summarised in table 3.

VISUAL PROGRESS

The visual level in the majority of children in groups I, II, and IV did not change during the period of study (table 4). Vision deteriorated in one child in group I who developed traumatic cataracts as a result of eye poking. In contrast, the visual level in the majority of group III improved, in two from very severe to moderately severe impairment and in two from moderately severe to mild; improvement has not been maintained in two of these patients who have both shown deterioration in visual acuity in later childhood.

Discussion

The study clearly shows that impaired intellectual potential and/or specific learning disability are more common when congenital retinal dystrophy is associated with additional medical problems. The influence of central nervous system malformation or degeneration and of dual sensory disability on a child's potential for mental development is expected. The poorer developmental prognosis of children with medical problems in other systems needs further consideration. Only one child in the series, the child with Leber's amaurosis and cardiomyopathy, had significant ill health during the study period; she remained moderately delayed even after successful treatment of her cardiac failure. With the exception of some of the neurodegenerative disorders, the enzymatic abnormalities in the congenital retinal dystrophies have yet to be identified.[5] The presence of disorder outside the visual system may reflect a more widespread disturbance of cellular function, expressed in some as intellectual impairment.

Lack of vision imposes major constraints on many aspects of development.[12] Parents are best able to implement a programme of developmental intervention[13] when content and confident of the future.[17] Uncertainty about developmental potential is likely to heighten parental anxiety and jeopardise development of a baby further. The finding that babies without, as opposed to with, additional medical problems are more likely to have good developmental potential strengthens the basis for developmental counselling about this group of conditions. Lessening the uncertainties surrounding a baby's future is likely to enable parents to play a more active part in promoting development.

Visual prognosis also differed among the subgroups. Except in children with Joubert's syndrome it was uniformly poor. This finding is supported by a study which evaluated a programme to promote cognitive, motor, and visual development in 58 babies with a variety of visual disorders; all five children with Leber's amaurosis failed to make visual progress whereas both children with Joubert's syndrome made progress.[14] Better preservation of visual evoked responses in the latter subgroup of CRD may have relevance.[2] Fielder, Fulton, and Mayer, however, recently reported significant visual improvement in three of five babies with Leber's amaurosis.[18]

Behavioural changes including autistic features appeared after a period of normal development in only two of the 20 children with Leber's amaurosis. In both this occurred during the second year in parallel with deceleration of development. Rogers and Newhart-Larson[19] using the Childhood Autism Rating Scale[20] and the Autism Behaviour Checklist[21] demonstrated significantly more characteristics of autism in five older boys with Leber's amaurosis than in five others who were congenitally blind from other causes. The appearance of autistic features was not associated with developmental deceleration in their cases; in the two children in this study it was associated with the development of a cognitive disorder and in this respect resembles more a pervasive disintegrative disorder.[22] In another study of 14 preschool cogenitally blind children, attending the DVC, deceleration occurred in two of eight with Norrie's disease and two of six with blindness due to other causes, such as anophthalmos, buphthalmos, and optic disc hypoplasia. This was accompanied by behaviour changes and some autistic features in two of the four.[16]

Our experience suggests that the onset of developmental and behavioural disorder in the second and third year of life is not disorder specific but found in a variety of conditions causing congenital blindness. It may be that the central nervous system is particularly vulnerable to the effects of blindness during the second year of life or to a combination of this plus adverse social/emotional stresses—the latter being documented in at least 50% of our cases of deceleration. Alternatively, cellular dysgenesis of variable degree within the central nervous system may be a feature of many of the conditions responsible for congenital blindness. Evidence that this is correct is growing—for example, in CHARGE association, Joubert's syndrome, and in septo-optic dysplasia.[23–25]

Our findings support the recommendations of Lambert *et al* that the presence of abnormal neurological signs or developmental delay in a child thought to have Leber's amaurosis should prompt full visual, neurological, and paediatric overview.[2] We would add that the finding of additional medical problems in a child with CRD is cause for caution and conversely their absence a cause for optism when counselling for developmental prognosis.

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Memory after treatment for acute lymphoblastic leukaemia

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Abstract

Long term survivors of acute lymphoblastic leukaemia (ALL) often experience cognitive difficulties, which may be related to impairment of memory function. Memory ability has been studied in a group of survivors of ALL along with sibling controls and in children who have received treatment for other forms of cancer. Children in the ALL group were found to have significant deficits in memory function in tasks which required the application of strategic planning behaviour. These deficits are potentially remediable by educational strategies.

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A majority of children now survive acute lymphoblastic leukaemia (ALL) but there has been an increasing awareness in recent years of the resultant intellectual deficits.[1 2] The assumption has been that cranial irradiation has been responsible for the decline in intellect and attempts have been made to replace it with systemic and intrathecal chemotherapy. There appears to be a global fall in intelligence quotient (IQ) in many children that may be largely due to deficits in memory function.[3] However, the details of where within the human memory system these deficits occur has not been previously identified. Normal memory function in both children and adults requires both active organisation and structuring of incoming material as well as the passive storage of information.[4]

A series of studies in Newcastle upon Tyne[5 6] has shown intellectual deficits in childhood ALL survivors when compared with both sibling controls and those treated for solid tumours when assessed using the British ability scales (BAS). The deficits seem to persist with time and are no fewer in patients who have been given 18 Gy cranial irradiation than in those given 24 Gy.[7] The shortfall seen in the ALL patients on the subtests of the BAS for 'speed of information processing and matrices' could suggest a deficit in the ability to formulate strategies or plans of action within the memory system. To clarify further the reasons for intellectual impairment a detailed assessment of memory function has been undertaken.

Table 1 Age at diagnosis and at assessment of leukaemia and tumour patients and their sibling controls

Subject group	No of subjects	Age at diagnosis (months)		Age at assessment (months)	
		Range	Mean (SD)	Range	Mean (SD)
ALL:					
18 Gy					
Patients	50	10–162	55·5 (36·6)	55–253	124 (41·1)
Siblings	41	—	—	48–219	112 (49·8)
24 Gy					
Patients	14	15–119	53·7 (36·8)	133–219	210 (42·9)
Siblings	11	—	—	112–291	202 (58·8)
Solid tumour:					
Patients	19	1–195	95·8 (63·1)	51–264	134 (71·7)
Siblings	13	—	—	61–270	151 (63·0)

Subjects and methods

Sixty four children in long term remission from ALL with 52 sibling controls, and 19 survivors of solid tumours with 13 siblings were studied. Of the children with ALL, 50 had received 18 Gy cranial irradiation and 14 had received 24 Gy. Further details are given in table 1. Each child was given a series of tests to determine intellectual and memory function. The BAS subtests appropriate to the child's age were administered and results of these have been given elsewhere.[7] In addition each received the following:

(1) The Cambridge automated neuropsychological test battery (CANTAB).[8] This is a set of computerised memory assessment procedures using a touch sensitive screen (Microvitec Touch Tech 501) on a BBC microcomputer. The tests selected were (a) the reaction time test (RTT), a test of choice reaction time; (b) delayed matching to sample test (DMTS), a measure of immediate memory for visual information; and (c) the delayed response test (DREP), which tests short term memory of material presented in a complex visual array.

(2) Immediate and delayed free recall test (IDFR). Four lists of 10 nouns were presented on a cassette recording at two speeds of presentation—that is, at one and two seconds per word. Two of the lists were presented at the beginning of the testing session and two at the end. The number of words correctly recalled immediately after presentation of each list was recorded (the immediate condition). After recalling both lists at each presentation, subjects were required to recall the first list again without a further chance to hear it (the delayed condition).

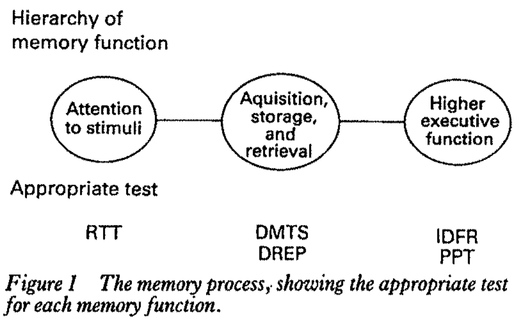
Hierarchy of memory function
Attention to stimuli
Aquisition, storage, and retrieval
Higher executive function
Appropriate test
RTT
DMTS
DREP
IDFR
PPT

Figure 1 The memory process, showing the appropriate test for each memory function.

(3) Picture probe task (PPT).[9] Six cards were presented face down in a row and the subject was asked to turn over each in turn, then replace it face down. A seventh card was then turned over and the subject was asked to select one of the original six cards which displayed the same household object. Differences in the number of cards correctly recalled may result from variations in the subjects' use of mnemonic devices such as a rehearsal strategy to aid recall. This possibility was investigated by calculating the mean intertime study times for each group of patients or siblings. This is the interval (in seconds) between the subject replacing one card and picking up the next. This task, unlike the other memory tasks, is self paced: the subject is in control of the rate of the presentation of the 'to be remembered' objects. This makes it possible to determine whether a rehearsal strategy is being employed. If the subject is using a cumulative rehearsal fast finish strategy, which would be the most appropriate mnemonic device for this task, then this can be seen when the interitem study times are plotted graphically.[10]

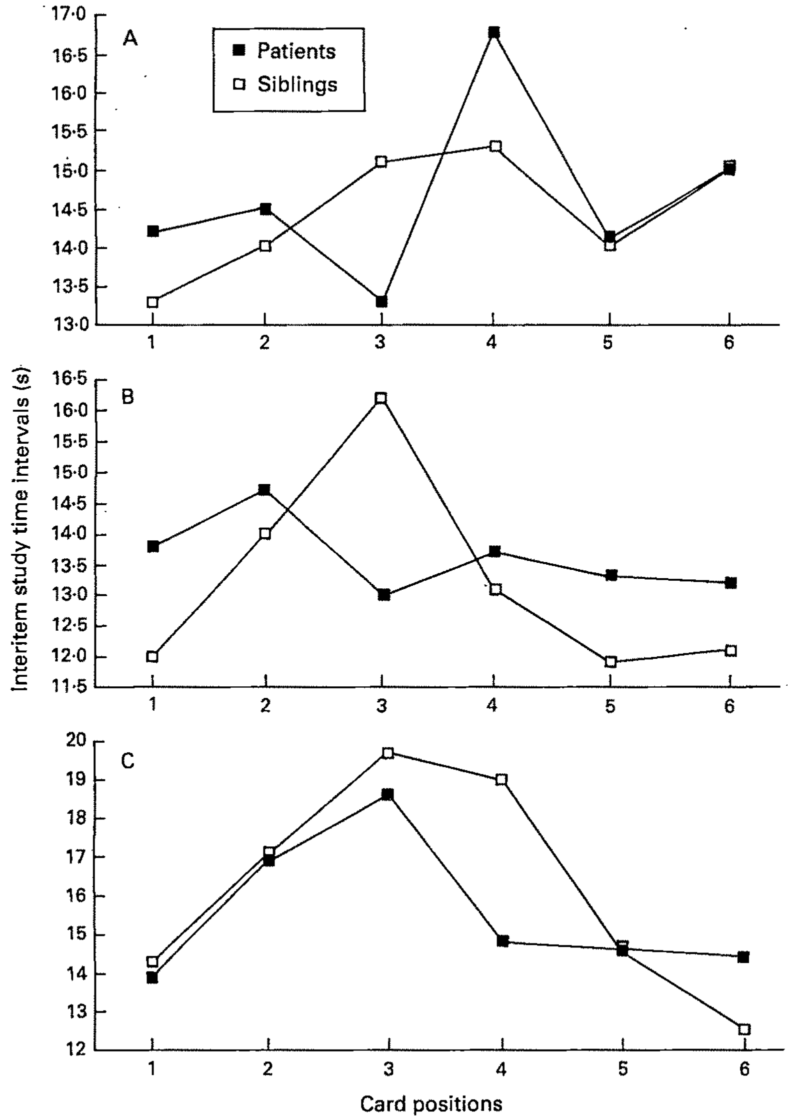

Figure 2 Mean interitem study times at each card position for patients and siblings in the leukaemia groups (A) 18 Gy and (B) 24 Gy and in the solid tumour group (C) during the picture probe task.

Figure 1 indicates which areas of the memory process each of the tasks is targeting. The median and mean scores for each test were calculated and comparisons were made between the different subject and sibling groups. The statistical test used was the analysis of variance, with age acting as a covariant where appropriate.

Results

The major findings for each of the tests are shown in table 2. For RTT, DMTS, and DREP there were no significant differences between subject groups and sibling controls. Similarly, when immediate recall in the IDFR test was examined no significant differences were found at either presentation speed. However, when the number of items correctly recalled during the delayed test in the IDFR was examined, the leukaemia patients in both the 24 Gy and 18 Gy groups were found to recall significantly fewer items than sibling controls (24 Gy, F=6, p=0·01; 18 Gy, F=4·6 p=0·05). There was no such difference in delayed recall in the group with solid tumours.

In the PPT an analysis of covariance showed that both of the leukaemia groups were found to recall significantly fewer items than their sibling controls (24 Gy, F=1·8, p=0·03; 18 Gy, F=5·0, p=0·01). No such difference was found in the solid tumour group. The interitem study time curves are shown in fig 2. The solid tumour

Table 2 Mean (SD) results for the tests on all groups, showing the reaction time, and the number or percentage of correct recalls

Tests	ALL at 18 Gy		ALL at 24 Gy		Solid tumour	
	Patients	Siblings	Patients	Siblings	Patients	Siblings
Attention:						
RTT (seconds)	70·7 (85·3)	70·6 (85·3)	32·3 (4·5)	32·5 (7·6)	44·8 (18·1)	38·2 (13·5)
Basic processes:						
DMTS (No)						
Simultaneous	9·0 (1·3)	9·0 (1·4)	9·9 (0·3)	9·7 (0·4)	9·1 (1·4)	9·0 (0·9)
0	7·3 (1·8)	7·4 (2·0)	8·7 (1·1)	9·1 (1·2)	7·7 (1·9)	7·3 (2·2)
4	6·5 (1·9)	6·9 (2·1)	8·4 (1·2)	8·5 (1·7)	7·3 (2·2)	6·3 (2·7)
12	6·0 (2·4)	6·7 (2·2)	8·5 (1·5)	8·7 (1·5)	5·9 (2·8)	7·1 (2·7)
DREP (% at level 8)	84	87	92	90	89	100
Executive function:						
IDFR (%): immediate at						
1 second	49	52	56	61	42	46
2 seconds	50	59	58	66	46	51
Delayed	22 *	27	20 *	36	22	26
PPT (no)	10·7 (2·7)*	11·9 (2·8)	11·2 (2·4)*	13·4 (1·8)	10·9 (4·0)	13·1 (3·4)

RTT reaction time test; DMTS, delayed matching sample test; DREP, delayed response test; IDFR, immediate and delayed free recall test; PPT, picture probe task.
*Indicating a significant difference in performance.

patients and all three sibling groups displayed the normal expected pattern if a cumulative rehearsal fast finish strategy is being employed.[10] However, both leukaemia groups show curves which suggests that no such strategy was being used. This is particularly evident at card 3 where those using a cumulative rehearsal strategy display an increase in time as the number of items to repeat increases to three, whereas the converse is true for the two leukaemia groups at this position.

Discussion

The results of the overall IQ as measured by the BAS in this group of patients has shown a clear deficit in both of the leukaemia groups when compared with their siblings but no such defict in patients with solid tumours.[7] Analysis of the component parts of the BAS suggested that deficits in abstract reasoning and planning might be, at least in part, responsible for the global reduction in IQ. The results shown here disaggregate the component parts of the memory and show that the deficit appears to lie in the most sophisticated part of the memory process—that is, the 'central executive'. The tests show no significant differences between patients and siblings in less sophisticated memory functions.

The results of the CANTAB reaction time test and the immediate conditions of the IDFR test show that attentional ability is not affected. Similarly, storage of material is not a problem as shown by the DREP test and the DMTS where all subjects demonstrated ability comparable with their siblings in spatial memory, list learning, visuospatial learning, pattern discrimination, and retention. Retrieval of information is not significantly lower for the leukaemia patients where the DMTS and DREP show ability to retrieve abstract material even over long delay periods.

The results of the delayed condition of the IDFR and the results of the PPT show a consistent deficit in the ALL groups. Figure 2 shows that at least one reason for this is that the children with ALL were not using a cumulative rehearsal strategy. A rehearsal strategy aids recall by transferring the items to be remembered from a memory buffer store into short term memory. If a rehearsal strategy is not employed, as soon as more information to be remembered is introduced (as in the immediate condition of the IDFR), the items already in the buffer store will be lost by a process known as 'retroactive interference' in which incoming material displaces information within the memory buffer.[11] Therefore subjects not manipulating items in their memory store will recall fewer items during a delayed condition.

Due to the fact that the two leukaemia groups are of unequal size (24 Gy, n=14; 18 Gy, n=50), and those children in the 24 Gy group are somewhat older and had been diagnosed longer, it would be inadvisable at the present time to assume that these two populations are a homogenous group. It is possible that the lack of differences between these groups may result from factors other than specific components of the irradiation treatment. Nevertheless, the children with ALL do appear to be displaying 'strategic unawareness', in other words the memory deficit present in the ALL population appear to be of metamemorial nature rather than a structural defect. The potential importance of these findings lies in the fact that children with this type of deficit may be amenable to intervention and training. Specific training to improve awareness of rehearsal strategies may well overcome some of the global deficits shown by many children who have survived ALL. Remediation may be attempted through the adoption of an intervention programme. Here, those children not using task appropriate memory strategies expected for their age could be identified during routine clinic visits using a simple battery of memory tasks. These children could then undergo a training programme. The programme would be designed to teach the adoption, maintenance, and generalisation of memory aids. Through this method an awareness of techniques such as labelling, that is, asking a child to name a remembered object, and rehearsal, as already mentioned, could be achieved. Attempts at remediation have been made among other groups exhibiting similar deficits with varying results.[12]

Overall treatment strategies for ALL are changing in an attempt to minimise intellectual damage. However, there are many survivors treated on previous regimens who could potentially be helped to optimum functioning.

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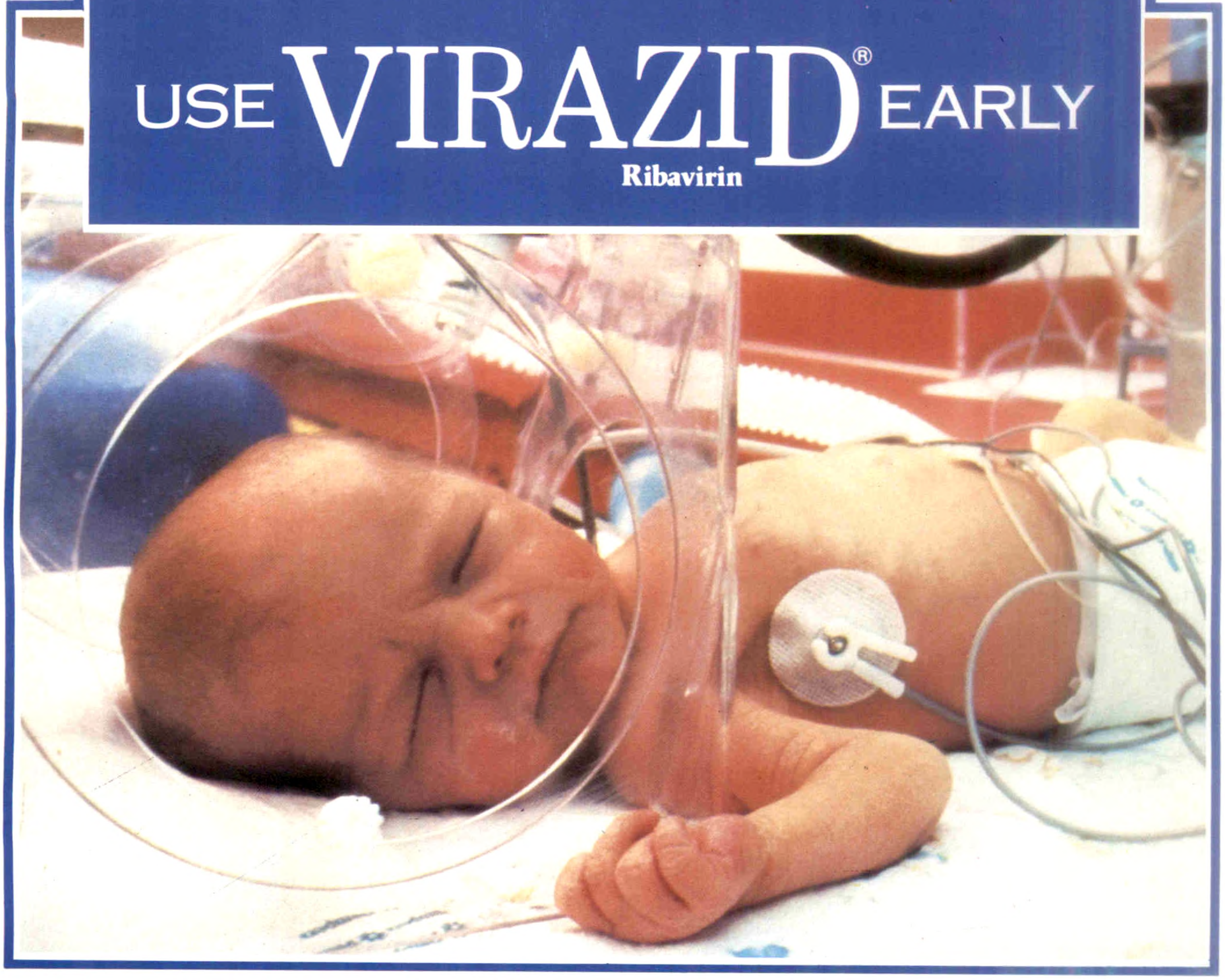

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What consistency of food is best for children with cerebral palsy who cannot chew?

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Abstract

Video recordings were made of 67 children with cerebral palsy and 64 able bodied children eating soft boiled ('non-mashed') and mashed potato. Those children with cerebral palsy who had no speech, presumed to have poor oral motor function, took significantly longer to eat non-mashed than mashed potato. Children with cerebral palsy, especially those with no speech, were more likely to cough or choke while eating non-mashed than mashed potato.

It is recommended that children with cerebral palsy who have poor oral motor function are offered food that they can eat with the least frustration or distress. This may also improve their dietary intake and state of nutrition.

Children with cerebral palsy often have difficulty eating.[1] They can take up to 18 times longer to eat a mouthful than normal children.[2] It is not surprising that many such children are emaciated.

It is not known what is the best type of food to offer children with cerebral palsy who have eating difficulty. They may be less likely to aspirate solid food.[3] Children with cerebral palsy, however, as well as normal children, take longer to eat solid than puréed food.[2]

It has been recommended that children with cerebral palsy should be weaned from purée to solid food.[4] It is not known whether or not this promotes the development of oral motor function.

It was the hypothesis of this study that children with cerebral palsy who had poor oral motor function, unlike normal children, would take significantly longer to eat soft solid food, than the same food after it had been mashed.

Subjects and methods

Seventy one children with cerebral palsy, as defined by Robinson *et al*,[1] were identified at two special schools. Four children were unavailable or unwilling to participate. The school speech therapists independently divided the children into three groups according to their ability to speak (table 1): those with normal or near normal speech (group I), those with poor speech (group II), and those with no speech (group III). Sixty four normal children were recruited from local mainstream schools for comparison (table 2).

Video recordings were made of all the children eating potato in their school dining area just before a main meal. The video camera was positioned about four metres from the children, who were thus aware of being recorded, but unaware of the purpose. Each child was given 10 g (1–2 teaspoons) of soft boiled potato ('non-mashed') and 10 g of this potato after it had been mashed. The potato had been cooked in lightly salted water but no butter or milk was added. The only difference therefore between the mashed and non-mashed potato was the texture. The potato was weighed on electric scales that were accurate to ±0·5 g. Random numbers were used to determine the order in which each child was served the two types of potato.[5] Children with cerebral palsy who could not feed themselves independently were assisted or fed by care givers familiar to them who used their knowledge of the children to determine the size of each spoonful offered. Every effort was made to avoid loss of spilled food.

The time taken by each child to eat 10 g of mashed and 10 g of non-mashed potato ('eating time') was measured by stopwatch from the video recording. The eating time was defined as the time from the beginning of the first mouthful until the 10 g of potato had been swallowed. Children with relatively good oral motor function were able to demonstrate that they had swallowed the potato. In the case of the more dependent children, the care givers feeding them were asked to indicate when the potato had been swallowed.

The eating times of children with cerebral palsy were measured twice by the author, at an interval of six weeks. The standard deviation of the differences between these pairs of eating times was taken to be a measure of intraobserver reliability. An independent colleague timed 10

Table 1 Numbers of children in each group with each main type of cerebral palsy

Type of cerebral palsy	*Group I*	*Group II*	*Group III*	*Total*
Hemiplegia/diplegia	14	1	0	15
Athetoid	2	3	5	10
Spastic quadriplegia±athetoid	7	10	25	42
Total	23	14	30	67

Table 2 Numbers of children with cerebral palsy in each group, and normal children, in each age range

Age range (years)	*Children with cerebral palsy*			*Normal children*
	Group I	*Group II*	*Group III*	
3–6	6	5	3	23
7–11	9	6	11	23
12–18	8	3	16	18
Total	23	14	30	64

randomly chosen children with cerebral palsy to provide a measure of interobserver reliability by a similar calculation.

The eating times for mashed and non-mashed potato were compared by the Wilcoxon signed rank test. This comparison was made separately for each group of children with cerebral palsy and for the normal group.

Children with cerebral palsy in group III (those with no speech) were compared with age and sex matched controls. The children with cerebral palsy were matched with the first suitable controls in order of recruitment. Age matching was to within a year for children aged 10 years or less, and to within two years for children aged over 10 years. The number of children with cerebral palsy in group III who took one and two minutes longer to eat non-mashed potato than mashed potato, and vice versa, was compared with the number of normal control children who did so. The χ^2 test was used to assess the significance of this difference.

Any coughing or spluttering seen on the video recording was noted. The number of children with cerebral palsy who coughed or spluttered while eating non-mashed potato was compared with the number who did so while eating mashed potato. The number of children with cerebral palsy in group III (those with no speech) who coughed and spluttered was compared to the number of children in groups I and II (those with speech) who coughed or spluttered. The χ^2 test was used to assess the significance of these differences.

Results

The standard deviation of the differences between the pairs of eating times of children with cerebral palsy, or intraobserver reliability, was 6·0 seconds. The standard deviation of the differences between the eating times of 10 randomly chosen children measured by the author, and the eating times of the same children measured by an independent observer, or interobserver reliability, was 11·7 seconds. Thus the maximum experimental error was taken to be ±11·7 seconds.

The children with cerebral palsy who had no speech (group III) had significantly longer eating times for non-mashed potato than for mashed potato ($p<0{\cdot}01$). Their eating times for non-mashed potato were on average nearly a minute longer than for mashed potato (table 3), well in excess of the maximum experimental error of ±11·7 seconds. In group III a significant number of children took two minutes longer to eat non-mashed than mashed potato (table 4).

Neither children with cerebral palsy who had speech (groups I and II) nor normal children had significantly longer eating times for non-mashed than for mashed potato.

Table 3 Mean times, in seconds, taken by children to eat 10 g of mashed and 10 g of non-mashed potato

	Children with cerebral palsy			Normal children
	Group I	Group II	Group III	
Mashed	38	92	134	29
Non-mashed	40	108	192	31

Table 4 Number of children who took one or two minutes longer to eat 10 g of non-mashed than 10 g of mashed potato and vice versa

	Group III	Normal children
Total No of children	30	30
No who took 1 minute longer to eat non-mashed potato	12*	0
No who took 1 minute longer to eat mashed potato	2	0
No who took 2 minutes or longer to eat non-mashed potato	5**	0
No who took 2 minutes longer to each mashed potato	1	0

By χ^2 *$p<0{\cdot}001$ and **$p<0{\cdot}01$.

Nine children with cerebral palsy coughed or spluttered while eating non-mashed potato, sometimes experiencing distress. Only two children with cerebral palsy coughed or spluttered while eating mashed potato; this difference is significant ($p<0{\cdot}05$). All the children who coughed or spluttered, except one, were in group III, a significant finding ($p<0{\cdot}01$). No normal child coughed or spluttered.

Discussion

Children with cerebral palsy who had no speech, presumed to have worse oral motor function as a group than those with speech, took significantly longer to eat soft solid food than mashed food. This difference in texture was too slight to affect either normal children or children with cerebral palsy who had speech.

Children with cerebral palsy are often malnourished. A likely cause is poor food intake, although exact measurement of food intake in children who spill and waste much of their food is difficult. There is evidence that children with poor oral motor skills are especially likely to be underweight.[6] We have also found that non-speakers were thinner and lighter than speakers (R D Croft, R O Robinson, M A Cockram, unpublished observations). This present study showed that non-speakers took on average six times longer to eat 10 g of soft boiled potato than normal children. This was almost a minute longer on average than it took them to eat mashed potato. It is likely therefore that the choice of food texture could significantly affect the dietary intake of children with poor oral skills, and as a result, their nutritional state.

Many of the severely affected children with cerebral palsy at Chailey Heritage Hospital have respiratory problems associated with eating or drinking. These children are mainly non-speakers. Some have reflux with aspiration and others have abnormalities of swallowing. Significantly more children in this study coughed or spluttered while eating non-mashed potato. On two occasions this coughing lasted several minutes and in one case the child became cyanosed and the study was discontinued. We have no prospective data on the serious long term complications of aspiration. The finding of this study is that children who cannot chew have more problems with lumps of food than mashed food and they sometimes experience distress that may be severe.

Younger children at Chailey Heritage Hospital with poor oral motor function receive oral motor therapy in groups, four times a week, as part of a conductive education programme. The oral motor therapy occupies about 10 minutes of each session. Older children, from about the age of 11, receive individual therapy as appropriate. Attention is paid to maintaining good seating and head position and practising lip closure, jaw control, breathing, swallowing, and tongue movements. Our impression is that this oral motor therapy is effective because we observe improvement in the speaking and eating skills, and a reduction in drooling, in new pupils who have been admitted to the hospital. There is however little research based evidence to confirm this. This study shows that there is a limit to what should be expected from oral motor therapy. Despite regular therapy as described above, many children with poor oral motor function will continue to be unable to chew. The practice at Chailey Heritage Hospital has therefore been modified. The most malnourished children with poor oral motor function are now given mainly mashed food, which can be mixed with gravy or sauces, which in turn could be fortified with protein-energy rich powders. The nutritional benefits are being evaluated.

Some individuals with cerebral palsy, in our experience at this hospital, continue to develop skills, such as improvements in speech, in their teens and even their late teens. For this reason, we do not recommend any specific age at which oral motor therapy should be abandoned. Practice with food of more difficult textures can form part of this therapy. The main meal, for those who cannot chew, should be mashed food.

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Gut regulatory peptides and intestinal permeability in acute infantile gastroenteritis

G R Lawson, R Nelson, M F Laker, M A L Ghatei, S R Bloom, A Aynsley-Green

Abstract

The plasma concentrations of seven gut regulatory peptides were measured in 11 infants suffering from acute gastroenteritis. Samples were taken at the time of the acute illness, upon reintroduction of feeding, and three months after recovery. These results were compared with controls. In the infants with diarrhoea, a massive increase in the fasting plasma mean (SEM) concentrations of enteroglucagon was found at the time of illness (1292 (312) *v* 79 (27) pmol/l), with concentrations of pancreatic glucagon, peptide tyrosine tyrosine, and motilin also being increased (17·8 (3·1) *v* 6·3 (1·1) pmol/l, 114·6 (15·2) *v* 37·0 (11·0) pmol/l, 217·6 (44·1) *v* 98·5 (18·3 pmol/l) respectively). The preprandial concentrations of motilin were found to be still increased at recovery (183·9 (35·4) pmol/l), but the concentrations of the other three peptides had returned to normal values. No differences in plasma concentrations of vasoactive intestinal polypeptide, neurotensin, or pancreatic polypeptide were found. An increased intestinal permeability was demonstrated at the time of diarrhoea by the urinary ratio of lactulose to mannitol, suggesting simultaneous gut damage.

The effects of regulatory peptides may be relevant to the pathophysiology of gastroenteritis in infants.

The efficient utilisation of food depends upon the integration of several aspects of gastrointestinal function. Food has to be propelled through the gut in an orderly sequence; local trauma caused by the passage of food leads to a need for mucosal regeneration. At appropriate times, digestive secretions enter the gut lumen, and the absorption of the nutrients thereafter depends upon adequate blood flow. The integration of the secretion of metabolic hormones is necessary to ensure homoeostasis. There is now good evidence to suggest that the secretion of regulatory peptides and their effects on target tissues through endocrine, paracrine, and neurocrine mechanisms have key parts to play in regulating these facets of digestive physiology. Moreover, massive postnatal surges of peptides have been described in neonates and have been proposed to have an important influence on the early adaptation of the gut to enteral feeding.[1–3] By 9 months of age the magnitude of the release of the gut regulatory peptides in response to feeding has diminished substantially from that seen in the neonatal period.[4]

Gut diseases in adults cause characteristic changes in the profiles of gut regulatory peptides, reflecting the nature and location of the disease, and the responses to therapy and recovery.[5] Acute infectious diarrhoea is a very common clinical condition, but although significant disturbances in the plasma concentrations of several of these peptides have been described in adults,[6] no information is available from studies on infants with gastroenteritis.

This study investigated changes which occurred in the circulating concentrations of gut regulatory peptides in infantile gastroenteritis, in order to determine the endocrine response that the gut mounts to infection in early life. To ascertain whether these changes were related to an alteration in gut mucosal function, intestinal permeability studies were performed using lactulose and mannitol. Similar studies have been used to assess mucosal integrity in coeliac disease and Crohn's disease,[7] and other diarrhoeal diseases including gastroenteritis,[8–10] where a damaged mucosa leads to an increased permeability.

Patients and methods

Eleven infants aged less than 2 years of age (range 3–15 months; mean 6·7) with acute gastroenteritis were studied. All had been previously well and none had a history of gastrointestinal disease. None of the infants was breast fed. They had all required admission to hospital for acute diarrhoea, this being defined as a change in bowel habit with three or more watery stools in the 24 hours before admission. Other medical and surgical causes of diarrhoea were excluded. The infants received glucose electrolyte solution (GES) by mouth until their symptoms had resolved, whereupon full strength feeds were introduced. Informed consent to investigate the infants was obtained from their parents and the study was approved by the joint university and hospital ethical committee.

Blood samples (2 ml) were taken through an intravenous cannula, being drawn at presentation and then at the time of initiation of refeeding, first just before starting to feed and then 60 minutes after the first milk feed. This always followed a feed of GES by at least three hours. Finally, a fasting sample was taken three months after recovery, between 6 am and 8.30 am immediately before the first morning feed and at least six hours after the previous feed. Stools were collected from all patients for bacteriological and virological investigation, including examination by electron microscopy. Blood was also drawn from 14 control infants of similar ages (range 2–22 months; mean 9·9)

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who were undergoing minor elective paediatric surgery. A preoperative fasting sample and one taken one hour after a postoperative milk feed were collected.

All blood samples were taken into chilled heparinised tubes containing 800 kallikrein-inactivating units of aprotinin (Trasylol), and the plasma was separated within 15 minutes of sampling and stored at −20°C until assayed. Plasma concentrations of enteroglucagon, pancreatic glucagon, peptide tyrosine tyrosine, motilin, vasoactive intestinal polypeptide, neurotensin, and pancreatic polypeptide were measured by specific and sensitive radioimmunoassay as described previously.[11–16] Intestinal permeability tests were performed using a dual marker, steady state method.[17] Lactulose and mannitol were chosen as markers because both are present in some infant feeds, both resist hydrolysis by intestinal enzymes, and both are passively absorbed by different routes across the intestinal wall, lactulose by paracellular pathways, and mannitol transcellularly. Neither marker is metabolised after uptake, and both are excreted wholly and solely in the urine where recovery approaches 100%.[18 19] When the two markers are combined in test feeds the effects on the results of variables such as rate of gastric emptying, intestinal transit, distribution within the body, and renal clearance, apply equally to both. Their urinary recovery is therefore a measure of passive intestinal permeability and thus of mucosal integrity.

After an initial urine sample had been taken on admission, infants received their fluid requirements with GES and then full strength, reconstituted granulated Cow and Gate Premium milk feeds containing a fixed ratio (5:1) of lactulose and mannitol. This was achieved by adding 5 ml of an aqueous solution containing lactulose (4 g/100 ml) and mannitol (0·8 g/100 ml) to every 100 ml of made up GES or milk feed. The reconstituted granulated feeds contained less than 1 mg/100 ml of either marker while GES contained none whatsoever. The addition of the aqueous solution produced concentrations of 200 mg lactulose and 40 mg mannitol per 100 ml of fluid. For comparison, ready to feed Cow and Gate Premium formula contains approximately 300 mg of lactulose and 20 mg of mannitol respectively (unpublished results). No adverse effects such as vomiting or alteration of bowel habit were seen with the use of these test feeds.

A steady state of marker input and output was achieved after 12 hours of test fluid intake, this being the day after admission in all but one infant who had intravenous fluids for 24 hours. Thereafter a daily random urine sample of at least 2 ml was obtained on each day of the admission. Urine samples were stored at −20°C with 0·1 ml 10% sodium merthiolate, and marker analysis was performed by gas-liquid chromatography.[7] Before discharge from hospital, the baby's mother was shown how to add the solution to reconstituted feed and was then given a supply of granulated feed and the marker solution. Infants were given this special feed for 48 hours before being reviewed four weeks after discharge, at which time a final random urine sample was collected. Solids were excluded from the diet for this period of two days in case they contained varying amounts of lactulose and mannitol.

Intestinal permeability was expressed as a urinary lactulose:mannitol excretion ratio calculated from amounts of the two markers present in the urine samples. A normal ratio of less than 0·55 was taken from a previous study undertaken in the same laboratory.[9]

Statistical analysis was performed by the nonparametric Wilcoxon's rank sum test, but data are expressed as mean (SEM) for convenience.

Results

GUT REGULATORY PEPTIDES

At presentation there was a massive increase in enteroglucagon concentrations ($p<0·001$ against control fasting and recovered fasting values) which persisted until the time of refeeding; there was no postprandial increment at that time. By the time of recovery the concentrations had returned to the normal range for age (fig 1, table 1).

There was an increase in pancreatic glucagon at presentation ($p<0·01$ against control fasting and recovered fasting concentrations) which was more pronounced ($p<0·001$) when fasting values just before refeeding were compared with recovered fasting or control fasting values (fig 2).

Peptide tyrosine tyrosine was found in high

Table 1 Table of mean (SEM) concentrations of gut regulatory peptides against the time of sampling

	Enteroglucagon (pmol/l)	*Pancreatic glucagon (pmol/l)*	*Peptide tyrosine tyrosine (pmol/l)*	*Motilin (pmol/l)*
At presentation	740 (144)	13·1 (1·6)	108·7 (25·7)	217·6 (44·1)
Fasting	1292 (312)	17·8 (3·1)	114·6 (15·2)	177·2 (45·3)
Postprandial	1319 (386)	15·4 (2·5)	121·1 (22·1)	101·4 (30·9)
Recovered fasting	122 (41)	5·8 (1·0)	21·7 (7·1)	183·9 (35·4)
Control fasting	79 (27)	6·3 (1·1)	37·0 (11·0)	98·5 (18·3)
Control postprandial	297 (106)	7·2 (1·4)	43·9 (11·1)	60·3 (10·8)

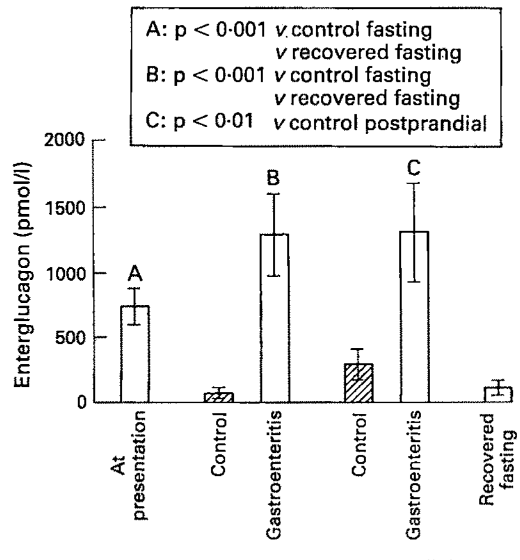

Figure 1 Mean (SEM) concentrations of enteroglucagon showing significant changes during and after gastroenteritis compared with control values.

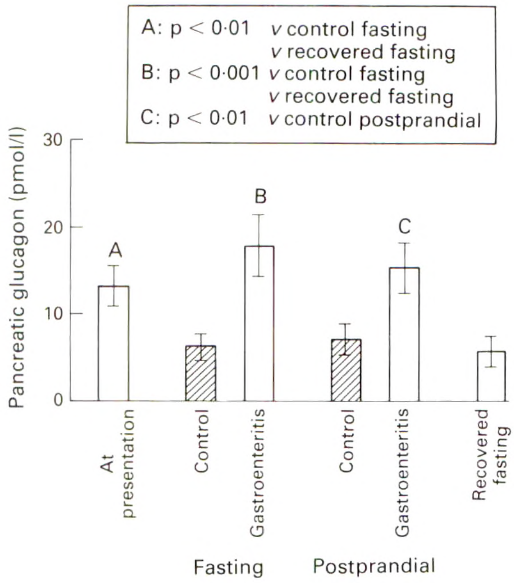

Figure 2 Mean (SEM) concentrations of pancreatic glucagon showing significant changes during and after gastroenteritis compared with control values.

concentrations at presentation and in postprandial samples ($p<0{\cdot}01$ when compared with recovered fasting and postprandial control samples respectively). Fasting concentrations before refeeding were similarly increased (fig 3) ($p<0{\cdot}001$ when compared with control and recovered fasting values). There was no statistical difference between the latter two.

At presentation, concentrations of motilin were found to be greater than fasting ($p<0{\cdot}02$) and postprandial ($p<0{\cdot}05$) values in control infants. Moreover, the concentrations at recovery were still significantly high compared with control values ($p<0{\cdot}05$ when compared with control fasting, and $p<0{\cdot}01$ when compared with control postprandial samples) (fig 4).

At no time were any significant differences seen between control subjects and infants with gastroenteritis in the concentrations of vasoactive intestinal polypeptide, neurotensin, or pancreatic polypeptide.

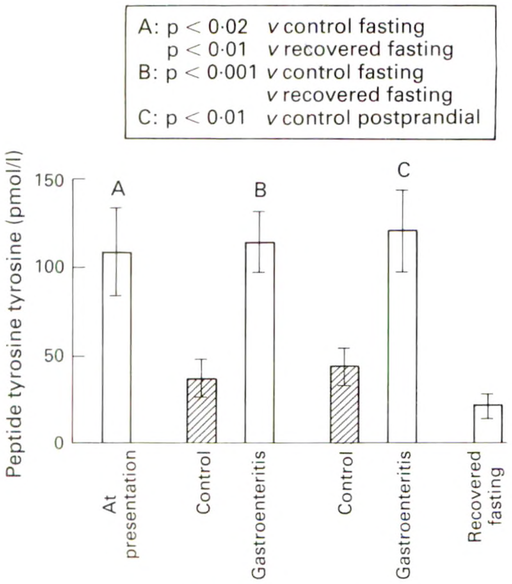

Figure 3 Mean (SEM) concentrations of peptide tyrosine tyrosine showing significant changes during and after gastroenteritis compared with control values.

INTESTINAL PERMEABILITY

The lactulose:mannitol ratio showed a significant increase on days 1 ($p<0{\cdot}01$), 2 and 3 ($p<0{\cdot}05$) but not on day 4 or thereafter, these results being compared with those at outpatient review (fig 5, table 2).

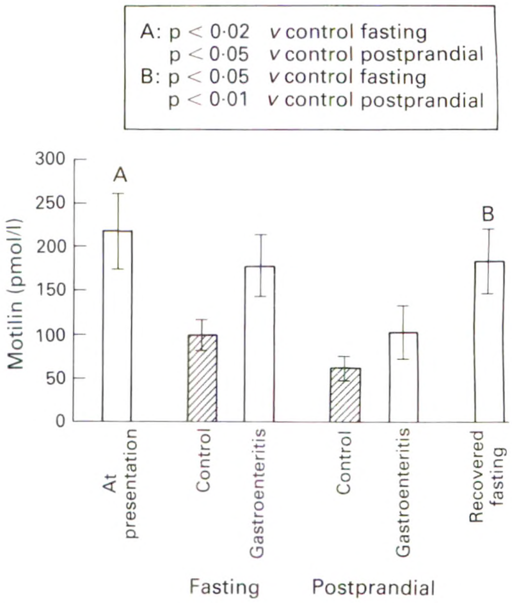

Figure 4 Mean (SEM) concentrations of motilin showing significant changes during and after gastroenteritis compared with control values.

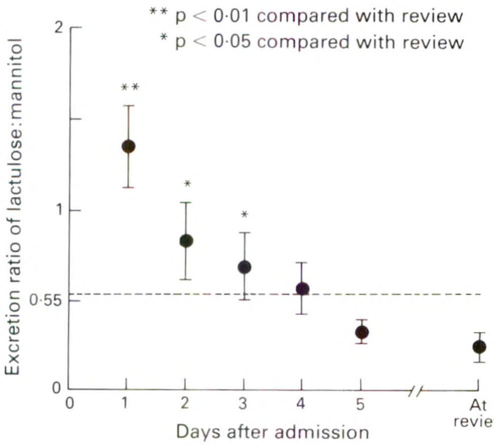

Figure 5 Excretion ratio of lactulose:mannitol in infants with acute gastroenteritis, expressed as mean (SEM).

Table 2 Table of lactulose:mannitol ratio against day of sampling, expressed as mean (SEM)

Day	*Lactulose:mannitol ratio*
1	1·35 (0·22)
2	0·83 (0·21)
3	0·69 (0·18)
4	0·57 (0·14)
5	0·33 (0·06)
At review	0·25 (0·07)

CLINICAL FEATURES

Infants had one to seven days of diarrhoea before admission (average 3·6) which continued for one to five days (average 2·1 days) after admission and treatment with GES. These latter figures excluded two infants with prolonged diarrhoea (see below). Stool reducing substances were never more than 0·25% in the studied infants and only one child had symptoms (of persistent vomiting) which necessitated intravenous fluids for 24 hours.

MICROBIOLOGY

Virological and bacteriological analyses of the stools revealed that six of the 11 infants had single pathogenic stool viruses, five with rotavirus and one with adenovirus. Two infants with adenovirus had a second infective organism which was isolated, one having rotavirus and the other enteropathogenic *Escherichia coli* type 0 124. No causative organism was isolated from the stool in three infants.

CHRONIC DIARRHOEA

Two infants in our study went on to have more prolonged diarrhoea which lasted for seven weeks and four weeks respectively. The first of these infants had an adenovirus and *E coli* type 0 124 isolated from the stools, and had particularly high values for fasting and postprandial plasma enteroglucagon (2472 and 3106 pmol/l), pancreatic glucagon (38 and 24 pmol/l) and peptide tyrosine tyrosine (173 and 190 pmol/l). After recovery the enteroglucagon concentration was 201 pmol/l which was well above the mean value, while the pancreatic glucagon and peptide tyrosine tyrosine had returned to normal values. The second infant with prolonged diarrhoea had rotavirus in stool samples but showed only one high value, that for fasting concentration of enteroglucagon, 1671 pmol/l, taken at the begining of his illness.

Discussion

The most dramatic finding from this study was the massive increase in concentration of enteroglucagon at the time of acute gastroenteritis. Enteroglucagon is found mainly in the ileum and colon. Raised circulating concentrations have been found in starved and refed rats,[20] in acute diarrhoea in adults,[6] as well as in patients with coeliac disease[21] and after ileal resection.[22] It is a hormone which is thought to stimulate mucosal growth and to slow down gastrointestinal transit,[23] and changes in its plasma concentrations are particularly impressive in the postnatal period when the normal neonate adapts to enteral nutrition.[24] Although it is difficult to extrapolate directly to the previous studies performed in adults with diarrhoea because of interassay variation in the measurement of these peptides performed in the same laboratory, when the mean concentrations in adults are compared with infants with diarrhoea, the concentrations in infants are some 15-fold higher. This may be due to a decreased plasma clearance mechanism for the hormone at this age, but it is more likely to be due to a gut endocrine system in babies which is more responsive to insults at a time of rapid growth and development of the gastrointestinal tract. Two infants in our study went on to have more prolonged diarrhoea, and both had particularly high concentrations when they first presented, but neither had unusually high permeability ratios. Thus the magnitude of enteroglucagon rise in diarrhoea may be related more closely to the extent of mucosal repair rather than to its actual damage.

In addition to the above hypotheses, it is known that viral enteritis causes mucosal damage particularly in the jejunum, while enteroglucagon is found in highest concentrations in the terminal ileum. The increase in enteroglucagon may thus be a compensatory mechanism to allow an increased uptake of nutrients which have not been absorbed in the damaged proximal gut.

Pancreatic glucagon is a stress hormone which has powerful effects on hepatic metabolism, but may also have secondary effects on gut motility and on gut growth. Although blood glucose concentrations were not measured in our study, hyperglycaemia is a well documented feature in acute gastroenteritis in infants.[25] This may well be related to the increased concentrations of pancreatic glucagon which were detected in our study, but not in the similar study in adults. The above findings may be because babies may have a more labile entero-insular axis, or are more severely stressed by their illness, and thus produce glucagon as a stress hormone.

The third hormone to demonstrate a considerable change during the course of the illness was peptide tyrosine tyrosine. It is known from infusion studies in adult men that concentrations of peptide tyrosine tyrosine in the physiological range have potent inhibitory effects on gastric secretion and emptying,[26] and also delay the mouth to caecum transit time.[27] As there is a surge of peptide tyrosine tyrosine concentrations in the neonate in the first month after birth during which time there are marked changes in gut motility and acid secretion, it has been suggested that this peptide may play an important part in the adaptation of the neonate to enteral feeding.[28] The apparently paradoxical increase of peptide tyrosine tyrosine in gastroenteritis may thus represent part of a feedback loop which would aid the eventual resolution of diarrhoea in infants with gastroenteritis. However, it is also known that plasma concentrations of peptide tyrosine tyrosine correlate quite well with intestinal cell proliferation after dietary manipulations in the animal model, and correlate very well with plasma enteroglucagon concentrations.[29]

The other hormone to show significant changes in concentrations during the illness was motilin, a peptide which is associated with the contraction of the gut.[30] It was the only hormone whose plasma values had not returned to normal concentrations three months after clinical recovery had occurred. None of the infants had experienced recent diarrhoea or had been symptomatic with intestinal motility problems including colic. These results may be related to the different degrees and type of fasting which the infants experienced when samples were taken during illness and then in recovery. However, the data could suggest that gastroenteritis in infants has a persisting effect on the secretion of this hormone, and further work is needed to determine the natural history and physiological consequences of these observations.

An enhanced intestinal permeability ratio confirmed that acute mucosal damage had occurred, this resolving in the days after admission. At review the ratio was always less than 0·55. The high ratio was in keeping with previously reported studies of gastroenteritis which have suggested that a loss of mucosal integrity and decreased mucosal surface area may explain these results.[8 9] Mucosal damage was demonstrated at the same time as the acute diarrhoea and the changes in circulating concentrations of enteroglucagon, pancreatic glucagon, peptide tyrosine tyrosine. Resolution of the increased intestinal permeability had occurred by one month, and of these gut regulatory peptides by three months, both being at times when no gastrointestinal symptoms were reported. Thus an association between acute gastroenteritis and mucosal damage with an alteration in gut regulatory peptides has been established.

The functional importance of the findings of raised plasma concentrations of enteroglucagon, pancreatic glucagon, peptide tyrosine tyrosine, and motilin in infants with gastroenteritis has yet to be defined. Our data strongly suggest that the infant gut reacts differently to that of adults during gastroenteritis, with an exaggerated increase in enteroglucagon and a persistent increase in motilin. They also suggest that plasma concentrations of gut regulatory peptides may act as markers of gut recovery. Further study is therefore needed in those children who develop chronic diarrhoea, particularly those with malnutrition, in whom the measurement of gut regulatory peptides might also be used to determine the effectiveness of treatment.

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Side effects: Are mainly CNS related. Aggression and psychosis have been reported and a previous history of psychosis or a behavioural problem appears to be a predisposing factor. Other reported events: drowsiness and fatigue, dizziness, nervousness, irritability, depression, headache and less commonly confusion, memory disturbance and vision complaints; also weight gain and minor gastrointestinal side-effects. Also in children excitation and agitation. Some patients may experience an increase in seizure frequency with vigabatrin, particularly those with myoclonic seizures. Tests have not revealed evidence of neurotoxicity in humans. Lab data do not indicate renal or hepatic toxicity. Decreases in SGOT and SGPT have been observed. Chronic treatment may lead to a slight decrease in haemoglobin.
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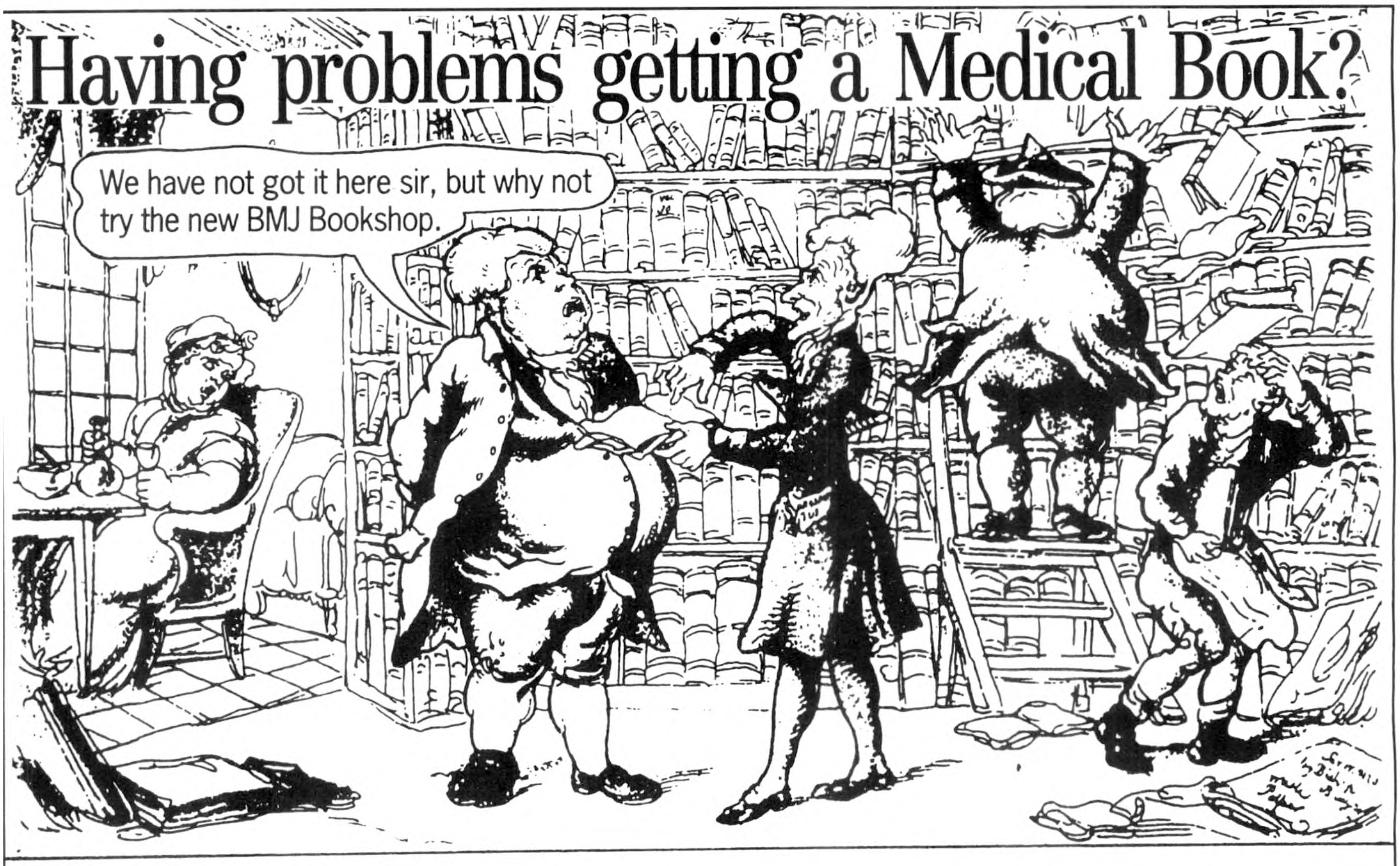
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Increased plasma tumour necrosis factor-α concentration in atopic dermatitis

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Abstract

Plasma tumour necrosis factor-α (TNF-α) was measured in 15 children with atopic dermatitis, 13 children with bronchial asthma, and 11 healthy controls. Plasma TNF-α concentration was increased in atopic dermatitis and the magnitude of the increase was correlated with the severity of the dermatitis but TNF-α concentration was not increased in bronchial asthma. A significant correlation was found between plasma TNF-α and plasma histamine concentrations in atopic dermatitis. The data suggest that the overproduction of TNF-α is associated with increased plasma histamine concentration, and might play a part in the pathophysiological mechanism of atopic dermatitis.

Atopic dermatitis is a chronic, pruritic, and inflammatory skin disease associated with several immunological abnormalities. These include an increase in serum IgE, decreased number of CD8+ T cells, reduced lymphocyte blastogenesis to mitogens, low incidence of positive skin tests, and depressed granulocyte and monocyte chemotaxis.[1]

Recent reports have suggested that the alteration of cytokine production may play a part in the pathogenesis of atopic dermatitis.[2 3] In the present study, plasma tumour necrosis factor-α (TNF-α) concentrations in atopic dermatitis and in bronchial asthma were compared with those in healthy controls. In addition, the association between plasma TNF-α and plasma histamine was investigated, as plasma histamine concentration has been reported to be increased in atopic dermatitis.[4 5]

Subjects and methods

SUBJECTS

Children visiting the paediatric department at Sumitomo Hospital were enrolled in this study. Fifteen patients with atopic dermatitis but without bronchial asthma (seven boys and eight girls) with a mean age of 3·3 years (range 1–15 years) were divided into three subgroups according to the severity of dermatitis (mild, moderate, or severe).[6] Thirteen patients with bronchial dermatitis but without atopic dermatitis (seven boys and six girls) with a mean age of 5·2 years (range 2–14 years) and 11 healthy controls (five boys and six girls) with a mean age of 4·6 years (range 3–10 years) were also studied. None of the patients was febrile, currently asthmatic, or receiving systemic steroids.

PLASMA AND SERUM

Fresh plasma was obtained from all subjects for the assay of histamine and TNF-α, and from patient's serum for IgE concentrations. Blood samples for plasma were collected in tubes containing EDTA, placed on ice immediately, and stored at −20°C until required.

TNF-α assay

Concentrations of TNF-α were determined using an immunoradiometric assay with a sensitivity of 1 pg/ml (IRE-Medgenix). Polypropylene tubes were coated with a combination of monoclonal antibodies to recombinant human TNF-α, which recognise distinct epitopes of TNF-α. Samples were incubated overnight in these tubes at room temperature with a mixture of ^{125}I-labelled anti-TNF-α antibody. After decantation, the bound fraction was counted with a gamma counter, and the concentration of TNF-α was expressed in terms of pg/ml with reference to a standard binding curve of recombinant human TNF-α.

HISTAMINE ASSAY

Concentrations of plasma histamine were determined using a new radioimmunoassay developed by Immunotech. Samples were placed into acylation tubes, to which acylation buffer was added, followed by centrifugation. ^{125}I-labelled acylated histamine was then added, after which the materials were centrifuged. Solutions were transferred to monoclonal antibody coated tubes, then incubated at 4°C overnight. After decantation, the bound fraction was counted with a gamma counter, and the concentration of histamine was expressed as nmol/l with reference to a standard binding curve of acylated histamine.

IgE QUANTIFICATION

Serum IgE concentrations were determined by solid phase radioimmunoassay (Phadebas IgE Prist, Pharmacia).

STATISTICAL ANALYSIS

All results are reported as means (SD). Student's *t* test was used to compare mean values.

Results

TNF-α CONCENTRATIONS IN PLASMA

As shown in fig 1, TNF-α was undetectable (<15 pg/ml) in plasma from most of the healthy controls, and TNF-α concentration was only slightly increased in plasma from bronchial asthma patients. In contrast, patients with atopic dermatitis showed increased TNF-α concentrations in plasma, and the magnitude of increase was correlated with the severity of the dermatitis.

HISTAMINE CONCENTRATIONS IN PLASMA

Figure 2 shows that plasma histamine concentration was higher in patients with atopic dermatitis (2·70 (1·09) nmol/l) than that in healthy controls (1·09 (0·35) nmol/l; p<0·001), and that the magnitude of increase was correlated with the severity of the atopic dermatitis.

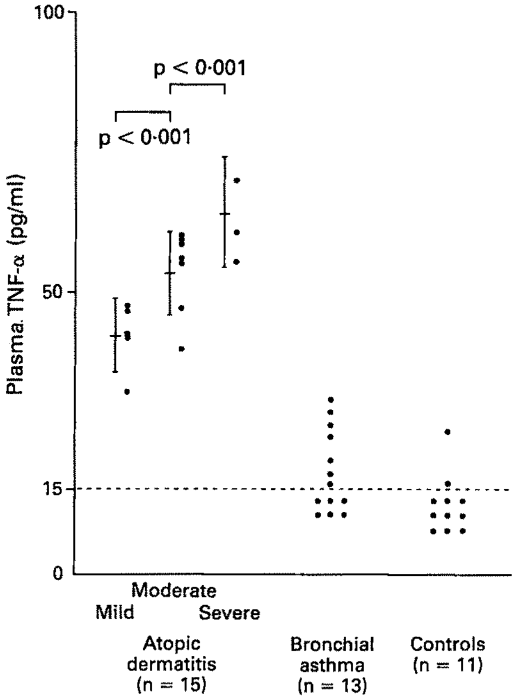

Figure 1 Plasma TNF-α concentrations in children with atopic dermatitis and with bronchial asthma, and in healthy controls. Dotted line indicates lowest detectable limit for TNF-α.

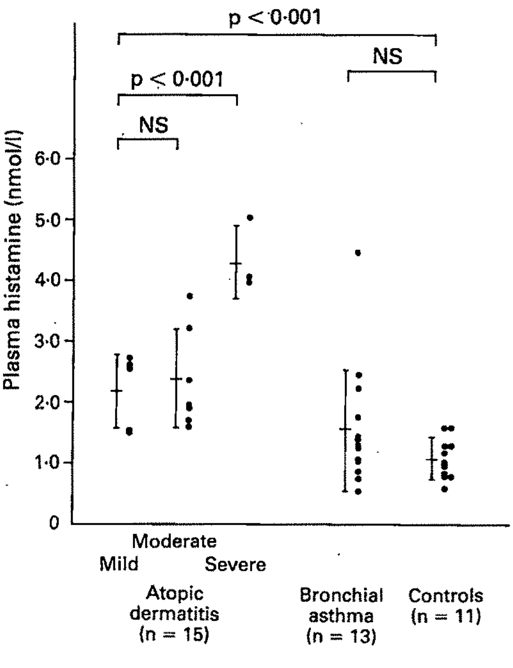

Figure 2 Plasma histamine concentrations in children with atopic dermatitis and with bronchial asthma, and in healthy controls.

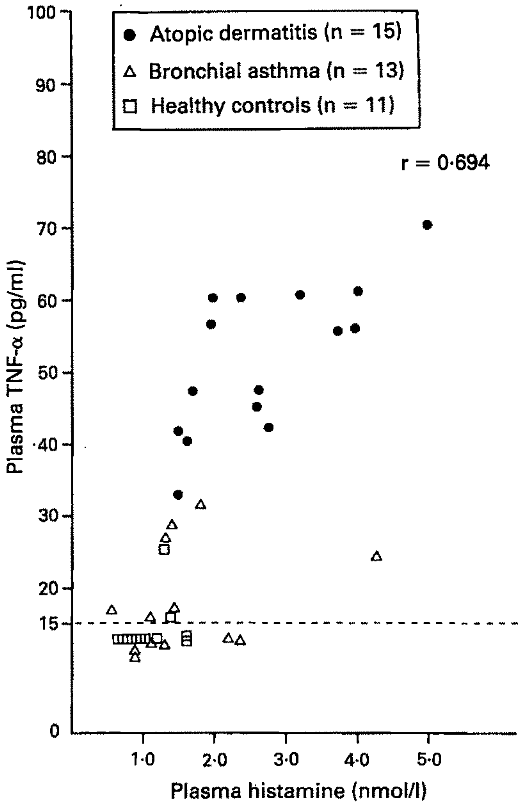

Figure 3 Relationship between plasma TNF-α and plasma histamine in children with atopic dermatitis and with bronchial asthma, and in healthy controls. Dotted line indicates lowest detectable limit for TNF-α.

RELATIONSHIP BETWEEN TNF-α AND HISTAMINE

As shown in fig 3, there was a significant correlation between concentrations of plasma TNF-α and plasma histamine in patients with atopic dermatitis (r=0·694; p<0·01), while there was no significant correlation between concentrations of plasma TNF-α and serum IgE in these patients (r=0·079).

Discussion

In the present study, we found that plasma TNF-α was increased in atopic dermatitis, and that the magnitude of increase was correlated with the severity of the dermatitis. The findings also show that in these patients there is an association between concentrations of plasma TNF-α and plasma histamine, but no relationship between concentration of plasma TNF-α and serum IgE.

TNF-α, a cytokine secreted by activated monocytes and macrophages, has been shown to produce a wide variety of biological effects in humans.[7–9] Some of these effects are associated with infection,[10] inflammation,[11 12] and immunoregulation.[13] According to a recent report, TNF-α is produced in keratinocytes,[14] and it may play a regulatory part in dermal–

epidermal interactions during wound healing, inflammation, and epidermal growth and differentiation.[15] After intravenous administration of TNF-α, a highly significant amount (30%) of it localises in the epidermis.[16] Along with granulocyte/macrophage colony stimulating factor and interleukin-1, TNF-α regulates Langerhans cell viability and differentiation,[17] and it also activates inflammatory cells such as neutrophils, eosinophils, macrophages, and fibroblasts.[18]

It is not known whether the increase in plasma TNF-α in our study was due to production by monocytes in peripheral blood or by macrophages and keratinocytes in the epidermis. The increased plasma TNF-α concentration suggests that the epidermal level is high, a condition which may increase the severity of atopic dermatitis. Although we could not determine the mechanism by which increased TNF-α concentration increases the severity of atopic dermatitis, it might be associated with plasma histamine, but is not associated with serum IgE.

Atopic dermatitis is a multifactorial disease, and hereditary, environmental, and immunological factors are all involved in its pathogenesis. The findings of the present study suggest that TNF-α may be related to the pathophysiological mechanism of atopic dermatitis.

We thank C Mishima and K Kanao for their expert technical assistance and Dr M Mayumi and Dr H Kimata for their useful discussion.

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Interleukin-2 production of lymphocytes in food sensitive atopic dermatitis

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Abstract

The proliferative responses of peripheral blood mononuclear cells (PBMC) to food antigens in 22 patients with food sensitive atopic dermatitis were significantly higher than the responses of healthy children and food sensitive children with immediate symptoms. Moreover, the activity of interleukin-2 (IL-2) in supernatants of food antigen stimulated PBMC cultures from patients with atopic dermatitis was significantly higher than that in healthy children and food sensitive children with immediate symptoms. The activity of IL-2 in culture supernatants of separated cell populations stimulated with food antigens from patients with atopic dermatitis and healthy children was investigated. The activity of IL-2 in supernatants of food antigen stimulated T cell cultures could be detected in patients with atopic dermatitis but not in healthy children. These results suggest that the increased IL-2 production after food antigen stimulation is due to increased T cell activity in food sensitive atopic dermatitis.

Food allergy clearly seems to play an aggravating part in some patients with atopic dermatitis, and the significance of IgE in the pathogenesis had been discussed.[1 2] Patients with atopic dermatitis caused by food allergens do not always have food specific IgE antibodies. Wraith *et al* have reported that 36% of foods causing 'non-immediate' symptoms give a negative radioallergosorbent test (RAST).[3] There is no clear correlation between the quantities of specific IgE antibodies and the nature and the severity of allergic symptoms, and patients may retain IgE antibodies for many years after they have ceased to suffer symptoms. Moreover, it is certain that atopic patients have abnormal responses in cell mediated immunity.[4–6] There have been some reports on proliferative responses of PBMC[7–9] and interleukin-2 (IL-2) production of inhaled antigen stimulated PBMC from allergic patients.[10 11] However, little has been reported on IL-2 production of food antigen stimulated PBMC from food sensitive patients. The aim of the present study was to find the proliferative responses of PBMC and T cells to food antigens and the IL-2 production of PBMC and T cells stimulated with food antigens in patients with atopic dermatitis who were sensitive to food allergens.

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Subjects and methods

SUBJECTS

Twenty two patients with atopic dermatitis were studied. Twelve were selected on the basis of clinical history and food challenges as being sensitive to hens' egg and 10 were selected as being sensitive to cows' milk. The 12 patients with atopic dermatitis who were sensitive to hens' egg ranged in age from 4 months–11 years (mean 2·5 years) and the 10 patients with atopic dermatitis were sensitive to cows' milk ranged in age from 4 months–10 years (mean 4·9 years). Food challenges were performed generally in the double blind, placebo controlled manner of Bock *et al*,[12] and in an open manner if there was a clear cut history of major allergic skin symptoms after ingestion of a specific food or if there was a chance of systemic anaphylaxis. Diagnosis of atopic dermatitis was defined by the criteria of Hanifin.[13] Cutaneous manifestations of most patients with atopic dermatitis appeared after two hours or more (usually within 48 hours) after hens' egg or cows' milk ingestion. The control group included 11 non-atopic healthy children without hens' egg or cows' milk sensitivity, ranging in age from 1–10 years (mean 4·2 years) (control group I), and seven hens' egg sensitive and nine cows' milk sensitive patients ranging in age from 11 months–13 years (mean 3·7 years) with urticaria, angio-oedema, acute gastroenteritis, and asthma (immediate symptoms) that appeared within one hour (usually within 15 minutes) after hens' egg or cows' milk ingestion (control group II). The RAST scores for hens' egg or cows' milk, proliferative responses of PBMC to food antigens, and IL-2 production of PBMC stimulated with food antigens were examined when diseases were diagnosed.

RAST

The RAST was performed as recommended by the Phadebas RAST test kit (Pharmacia).[14] Hens' egg and cows' milk discs were supplied by Pharmacia. RAST results were scored 0 to 4+ by comparison with serially diluted reference sera (Pharmacia) graded A to D (that is, a serum <D=0, between D and C=1+, and >A=4+). RAST scores of 2+, 3+, and 4+ were recorded as positive.

CELL SEPARATION AND CULTURE

Blood was taken into preservative free heparin and was separated by gradient centrifugation with the use of Ficoll-Paque (Pharmacia). PBMC were harvested from the interface and washed three times in phosphate buffered saline. To remove adherent cells, 2–5×10^7 PBMC were incubated in 20 ml of culture medium consisting of Roswell Park Memorial Institute (RPMI) medium 1640 supplemented with 15% pooled human AB positive serum, penicillin (100 U/ml), streptomycin (100 μg/ml), and L-glutamine (2 mM) in 75 cm^3 tissue culture flasks (Falcon) for 2–3 hours at 37°C. Non-adherent cells were recovered and were separated into a T cell enriched population and a B cell enriched population by the rosetting method with neuraminidase treated sheep red blood cells (SRBC), after which they were subjected to centrifugation over Ficoll-Paque[15] and a nylon wool column.[16] The rosetted cells were collected from the bottom, recovered by lysis of the SRBC in an isotonic ammonium chloride buffer for 10 minutes at 4°C, passed through the column, and washed three times with phosphate buffered saline. These cells were mainly T cells (CD3+>98%). Non-rosetted cells were collected from the interface and passed through the column. They were used as B cells (72% CD20+, 2% CD3+, and 2% CD14+). The adherent cells were harvested by a rubber policeman and washed three times with phosphate buffered saline. PBMC, T cells with adherent cells, and B cells with adherent cells were separately cultured at 1×10^6/ml in RPMI 1640 culture medium supplemented with 15% pooled human AB positive serum. Cultures were performed in triplicate at 0·2 ml per well in round bottomed microtest plates or culture test tubes with or without food antigens (A/S Nunc) at 37°C in a humidified atmosphere containing 5% carbon dioxide for 3–5 days.[7] Food antigens, ovalbumin (Wako Junyaku), and bovine serum albumin (Wako Junyaku) were separately diluted in culture medium and were added in final concentrations of 0·25 μg/ml, 2·5 μg/ml, and 25 μg/ml, respectively.

DNA synthesis was measured by adding 0·5 μCi tritiated (^{3}H)-thymidine per well four hours before harvesting onto glass fibre filters. ^{3}H-thymidine incorporation was measured by liquid scintillation counting as counts per minute (cpm) and the results were expressed as the mean of triplicate. To compare responses between individuals, we expressed the results as a stimulation index (SI) using the following formula:

$$SI=\frac{\text{cpm in cultures stimulated with food antigens}}{\text{cpm in unstimulated cultures}}$$

On the other hand, culture supernatants in the culture test tubes were spun to remove cells after three days and stored frozen at −40°C until measurement of the activity of IL-2.

MEASUREMENT OF THE ACTIVITY OF IL-2

The biological activity of IL-2 was determined by proliferation of cells from a mouse T cell line, NKC-3, which was highly dependent on IL-2 activity for growth. NKC-3 was a gift from Takeda Chemical Industries Co Ltd. Cells were cultured at 6×10^5/ml in RPMI 1640 culture medium with 20% heat inactivated fetal calf serum in round bottomed microtest plates in triplicate at 50 μl per well. Cultures were performed with 50 μl culture supernatant and 50 μl RPMI 1640 culture medium in a humidified atmosphere with 5% carbon dioxide for 24 hours, and were then pulsed with 0·5 μCi ^{3}H-thymidine per well four hours before harvesting. To compare responses between individuals we expressed the results as a SI using the following formula:

$$SI=\frac{\text{cpm in cultures with supernatants of food antigen stimulated PBMC}}{\text{cpm in cultures with supernatants of unstimulated PBMC}}$$

STATISTICS

Student's *t* test was used for the comparison of SI in different groups. The comparison of RAST scores was assessed by χ^2 analysis.

Results

RAST SCORES

The results of RAST scores, proliferative responses of PBMC and the activity of IL-2 for control group I, control group II, and patients with atopic dermatitis are presented in tables 1 and 2. The RAST values for hens' egg of patients with atopic dermatitis with hens' eggs sensitivity were significantly ($p<0·01$) lower than the RAST values of control group II. Although the RAST values for cows' milk of patients with atopic dermatitis with cows' milk sensitivity tended to be lower than the RAST

Table 1 Results of RAST scores for hens' egg sensitivity, proliferative responses of PBMC to ovalbumin, and the activity of IL-2 in culture supernatants of PBMC stimulated with ovalbumin for control group I, control group II, and patients with atopic dermatitis

Group	*No of subjects*	*Mean (SD) age (years)*	*RAST scores for hens' eggs (%)**					*Mean (SD) proliferative responses of PBMC to ovalbumin (SI)*	*Mean (SD) IL-2 activity (SI)*
			0	*1*	*2*	*3*	*4*		
Control group I (healthy children)	7	4·3 (2·8)	7	0	0	0	0	1·25 (0·38)	0·99 (0·41)
						(0)*			
Control group II (immediate allergic symptoms to hens' egg)	7	6·2 (6·4)	0	0	4	0	3	1·46 (0·67)	1·14 (0·33)
						(100)*			
Atopic dermatitis (sensitivity to hens' egg)	12	2·5 (3·5)	9	0	3	0	0	3·25 (1·99)†	2·53 (0·87)‡
						(25)*			

*Cases with positive RAST score/total cases.

†The proliferative responses of PBMC to ovalbumin in patients with atopic dermatitis sensitive to hens' egg were significantly higher than control group I ($p<0·005$) and II ($p<0·01$).

‡Activity of IL-2 in supernatants of ovalbumin or stimulated PBMC cultures from patients with atopic dermatitis sensitive to hens' egg were significantly higher than control group I and II ($p<0·005$).

Table 2 Results of RAST scores for cows' milk sensitivity, proliferative responses of PBMC to bovine serum albumin, and the activity of IL-2 in culture supernatants of PBMC stimulated with bovine serum albumin for control group I, control group II, and patients with atopic dermatitis

Group	*No of subjects*	*Mean (SD) age (years)*	*RAST scores for cows' milk (%)**					*Mean (SD) proliferative responses of PBMC to bovine serum albumin (SI)*	*Mean (SD) IL-2 activity (SI)*
			0	*1*	*2*	*3*	*4*		
Control group I (healthy children)	4	4·0 (4·2)	2	2	0	0	0	1·11 (0·30)	0·83 (0·81)
						(0)*			
Control group II (immediate allergic symptoms to cows' milk)	9	1·7 (0·9)	0	3	4	2	0	1·12 (0·42)	1·25 (0·59)
						(67)*			
Atopic dermatitis (sensitivity to cows' milk)	10	4·9 (4·0)	7	0	2	1	0	2·42 (1·24)†	3·23 (1·49)‡
						(30)*			

*Cases with positive RAST score/total cases.

†The proliferative responses of PBMC to bovine serum albumin in patients with atopic dermatitis sensitive to cows' milk were significantly higher than control group I and II ($p<0·005$).

‡Activity of IL-2 in supernatants of bovine serum albumin stimulated PBMC cultures from patients with atopic dermatitis sensitive to cows' milk were significantly higher than control group I and II ($p<0·005$).

values of control group II, there was no significant difference.

PROLIFERATIVE RESPONSES OF PBMC TO OVALBUMIN OR BOVINE SERUM ALBUMIN

The proliferative responses of PBMC to ovalbumin in patients with atopic dermatitis who were sensitive to hens' egg were significantly higher than those of either control group I or control group II ($p<0·005$, $p<0·01$, respectively; table 1). Similar results were seen in cows' milk allergy, as shown in table 2. The proliferative responses of PBMC to bovine serum albumin in patients with atopic dermatitis who were sensitive to cows' milk were significantly higher than those of either control group I or control group II ($p<0·005$, respectively). These results suggest that the proliferative responses of PBMC to ovalbumin or bovine serum albumin have a significant value in patients with atopic dermatitis who are sensitive to hens' egg or cows' milk. We have previously reported such findings.[7]

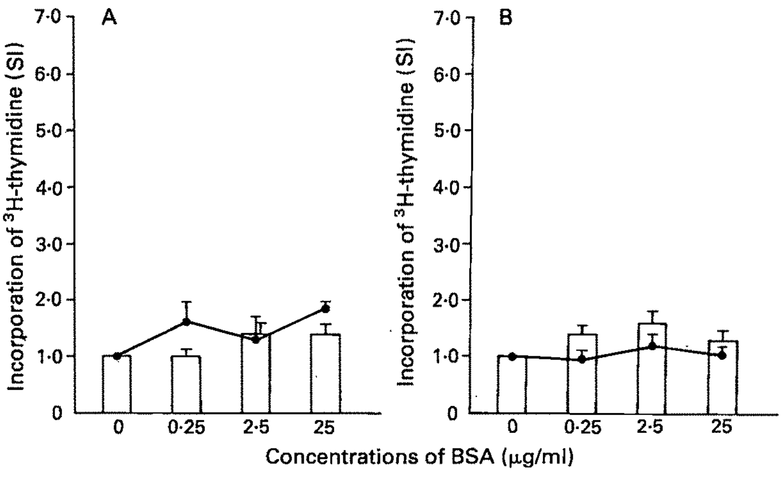

Figure 1 Proliferative responses of T cells and B cells to bovine serum albumin (BSA), and IL-2 production in BSA stimulated T cell and B cell cultures from a healthy child. (A) The line indicates the proliferative responses of T cells with adherent cells to BSA. The columns indicate the activity of IL-2 in culture supernatants of BSA stimulated T cells with adherent cells. (B) The line indicates the proliferative responses of B cells with adherent cells to BSA. The columns indicate the activity of IL-2 in culture supernatants of BSA stimulated B cells with adherent cells. Each value is the mean of triplicate and each bar indicates 1 SD.

IL-2 PRODUCTION IN OVALBUMIN OR BOVINE SERUM ALBUMIN STIMULATED PBMC CULTURES

The activity of IL-2 in supernatants of ovalbumin stimulated PBMC cultures from patients with atopic dermatitis who were sensitive to hens' egg was significantly higher than that in either control group I or control group II ($p<0·005$, respectively; table 1). Similarly, the activity of IL-2 in supernatants of bovine serum albumin stimulated PBMC cultures from patients with atopic dermatitis who were sensitive to cows' milk was significantly higher than that in either control group I or control group II ($p<0·005$, respectively; table 2).

IL-2 PRODUCTION IN OVALBUMIN OR BOVINE SERUM ALBUMIN STIMULATED T CELL OR B CELL CULTURES

We investigated the proliferative responses of PBMC, T cells with adherent cells, and B cells with adherent cells to ovalbumin or bovine serum albumin and IL-2 activity of culture supernatants in two randomly selected patients whose clinical manifestations of atopic dermatitis were severe and in two age matched healthy children. One of the two patients with atopic dermatitis was sensitive to hens' egg and the other was sensitive to cows' milk. The proliferative responses of T cells with adherent cells and B cells with adherent cells to bovine serum albumin and IL-2 activity of culture supernatants from a healthy child who is not sensitive to cows' milk are shown in fig 1. Both T cells with adherent cells and B cells with adherent cells did not respond to bovine serum albumin. Furthermore, IL-2 activity could not be detected in culture supernatants of bovine serum albumin stimulated T cells with adherent cells or B cells with adherent cells. The results for a patient with atopic dermatitis who is sensitive to cows' milk are shown in fig 2. T cells with adherent cells responded to bovine serum albumin, whereas B cells with adherent cells did not respond. IL-2 activity could be detected in culture supernatants of bovine serum albumin stimulated T cells with adherent cells; however, it could not be detected in culture supernatants of bovine serum albumin stimulated B cells with

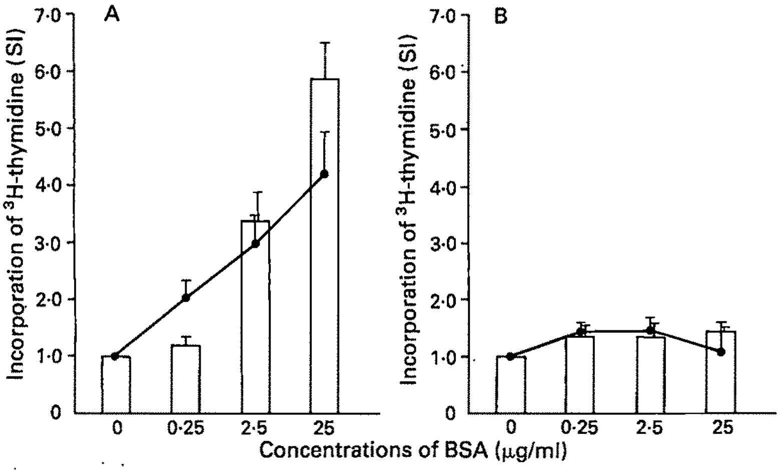

Figure 2 Proliferative responses of T cells and B cells to bovine serum albumin (BSA), and IL-2 production in BSA stimulated T cell and B cell cultures from a patient with atopic dermatitis who is sensitive to cows' milk. (A) The line indicates the proliferative responses of T cells with adherent cells to BSA. The columns indicate the activity of IL-2 in culture supernatants of BSA stimulated T cells with adherent cells. (B) The line indicates the proliferative responses of B cells with adherent cells to BSA. The columns indicate the activity of IL-2 in culture supernatants of BSA stimulated B cells with adherent cells. Each value is the mean of triplicate and each bar indicates 1 SD.

adherent cells. These results suggest that IL-2 production was only recognised in culture supernatants of bovine serum albumin stimulated T cells with adherent cells which had significantly responded to bovine serum albumin in a cows' milk sensitive patient with atopic dermatitis. The results of IL-2 activity in separated cell population cultures of a patient with atopic dermatitis with hens' egg sensitivity and a healthy child are shown in table 3. The results shown in table 3 are the same as those in figs 1 and 2. Consequently, the increased IL-2 production after food antigen stimulation seemed to be due to increased T cell activity.

Discussion

IL-2 was first recognised as a substance produced by T cells that had the ability to help support normal T cell proliferation in tissue culture.[17 18] Recently it was discovered that IL-2 promotes the proliferation of activated T cells[19] as well as B cells.[20 21] IL-2 acts by binding with IL-2 receptors on T cells and B cells, as well as natural killer cells. After antigen or mitogen activation of T cells, the cells begin to express an IL-2 receptor that appears within the first several hours after activation. Maximum expression occurs two to three days later followed by a decline in IL-2 receptor expression.[22] IL-2 production has generally been shown to be a function of OKT4+ T helper cells,[23] although another report suggests that, when stimulated by concanavalin A, OKT+8 cells may also produce IL-2.[24] Rawle *et al* have reported that IL-2 production was detected in supernatants of antigen P_1 stimulated T cell cultures from *Dermatophagoides pteronyssinus* sensitive patients.[10] In other studies, 'lymphocyte mitogenic factor' was reported in three day supernants of PBMC cultures of allergic patients proliferating in response to grass pollen.[11] Mosmann *et al* have reported that mouse helper T cell clones fall into two main groups (TH1 and TH2), defined primarily by differences in the pattern of lymphokines synthesised.[25 26] TH1 clones synthesise IL-2, interferon γ, and lymphotoxin, whereas these lymphokines are not detectably expressed in TH2 clones. Conversely, only TH2 clones synthesise detectable amounts of IL-4 and IL-5. TH1 clones also cause effective delayed type hypersensitivity reactions.[25 26]

In this study, proliferative responses of both PBMC and T cells to food antigens were recognised. Moreover, IL-2 production of PBMC and T cell cultures stimulated with food antigens was detected in patients with atopic dermatitis who were sensitive to food allergens. These results suggest that the increased IL-2 production after food antigen stimulation is due to increased T cell activity in patients with atopic dermatitis who are sensitive to food allergens.

We are grateful to Central Research Division, Takeda Chemical Industries Ltd for supplying cells, NKC-3, and to Misses Yukiko Hirano, Ryo Takenaka, and Tsukako Kameyama for the culture assistance.

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Table 3 Results of proliferative responses and the activity of IL-2 in culture supernatants from separated cell populations stimulated with ovalbumin in a patient with atopic dermatitis and a healthy child

	Serum IgE (U/ml)	*RAST scores for hens' egg*	*Proliferative responses to ovalbumin (SI)*			*IL-2 activity in culture supernatants (SI)*	
			Unseparated PBMC	*T+Ad**	*B+Ad†*	*T+Ad**	*B+Ad†*
Healthy child	38	0	1·63	1·63	1·06	1·21	1·37
Patient with atopic dermatitis (sensitive to hens' egg)	150	2	ND	4·30	1·01	2·68	0·81

*T cells with adherent cells.
†B cells with adherent cells.
ND, not done.

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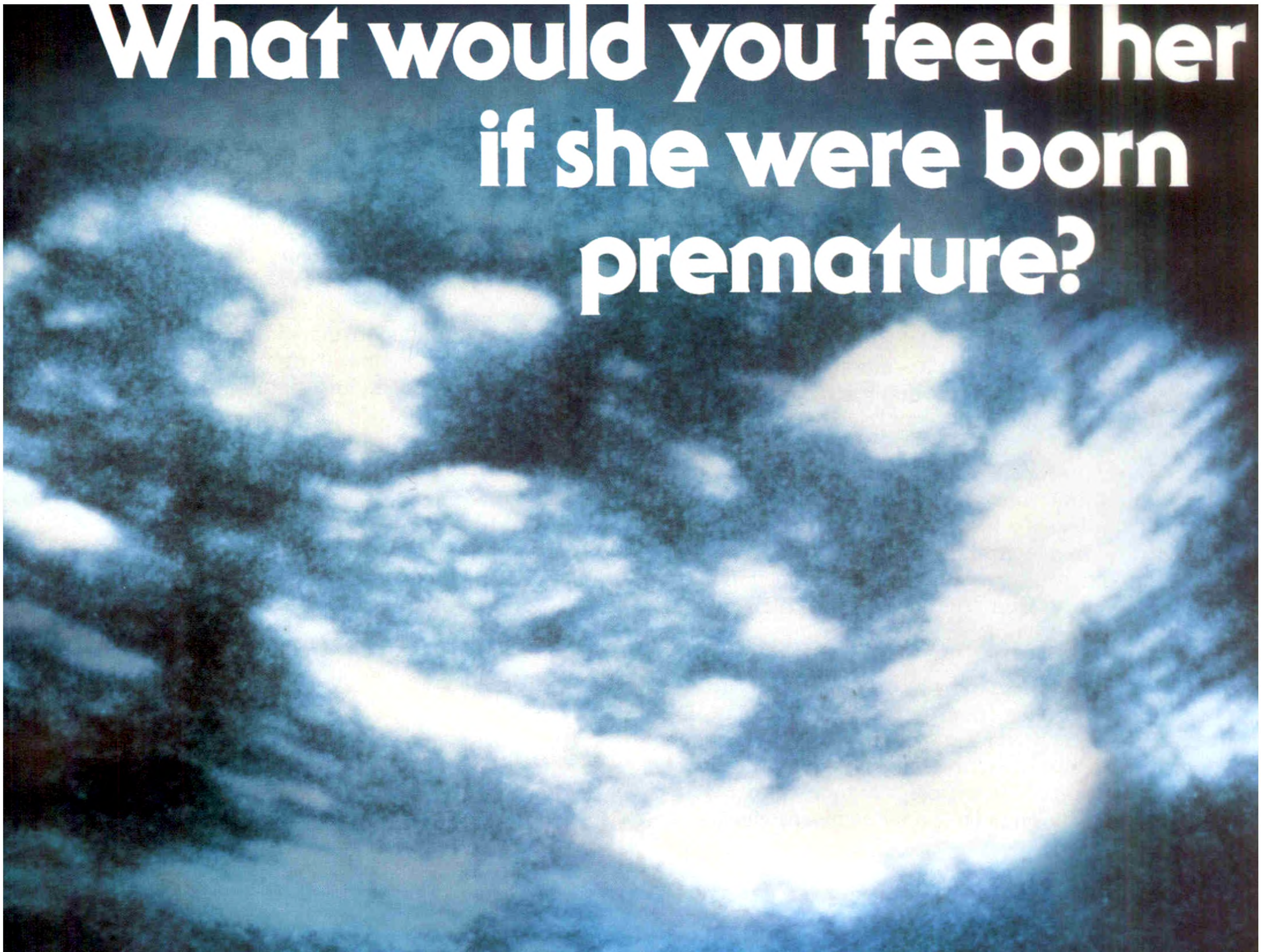
What would you feed her if she were born premature?



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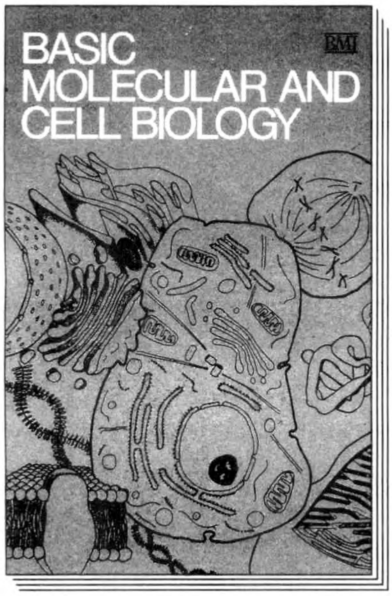

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Archives of Disease in Childhood 1992; 67: 285–288

Inhaled budesonide for chronic wheezing under 18 months of age

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Accepted 30 October 1991

Abstract

The role of budesonide in controlling chest symptoms in infants was assessed. It was administered from a metered dose inhaler into a large volume spacer (Nebuhaler) with attached Laerdal mask. Twenty nine infants were recruited into a double blind crossover trial. Five defaulted. The remaining 24 (mean age 11 months) were assessed for the tolerance of the device, adverse effects, treatment failures, parental opinion, and daily symptom and treatment records. Twenty tolerated the modified Nebuhaler. One developed meningitis on placebo. Two experienced exacerbations on placebo. Eleven of 18 parents whose children completed the maximum treatment preferred budesonide to placebo and one preferred placebo. Mean symptom scores on budesonide were better than on placebo for the 15 children with complete symptom records. Fewer bronchodilator doses were used while taking budesonide. Our findings indicate that budesonide given in this way is an effective treatment for infants who may need prophylaxis for their wheezing.

Although very common, wheezing has proved very resistant to treatment in infancy.[1] There is little evidence that oral therapy with β_2 stimulants,[2] theophylline,[3] or even steroids,[4] has any effect on the natural history of wheezing episodes in the first year of life. There remains considerable dispute whether inhaled β_2 stimulants improve lung function in infancy,[5-8] and only studies using ipratropium bromide have consistently documented a response, and then in less than 50% of infants.[9-11] Nebulised sodium cromoglycate does not appear to have a useful prophylactic effect until the child is over the age of 1 year.[10 12]

Table 1 Details of infants enrolled

Subject No	*Age (months)*	*Sex*	*Gestation (weeks)*	*Birth weight (g)*	*Neonatal respiratory problems*	*Atopic first degree relatives*
1	9·3	F	37	3880	None	Yes
2	11·0	F	40	2950	None	Yes
3	17·4	M	40	3400	None	Yes
4	4·1	M	40	3660	None	No
5	12·4	M	36	3090	None	No
6	16·4	M	40	2840	None	Yes
7	7·0	M	30	1080	Pneumonia	No
8	11·5	M	27	1070	BPD	Yes
9	12·5	M	38	2890	None	N/A
10	15·1	M	35	1660	None	No
11	12·8	M.	38	3520	None	Yes
12	13·1	M	40	2890	None	No
13	5·9	F	36	2890	None	Yes
14	12·1	F	40	3150	None	Yes
15	10·3	M	40	3910	None	No
16	11·1	M	40	3200	None	Yes
17	17·2	M	32	1550	BPD	Yes
18	6·5	M	38	2980	None	Yes
19	9·4	M	32	1360	None	No
20	10·6	M	36	2840	None	Yes
21	9·0	M	34	2100	RDS	Yes
22	12·1	F	42	3150	None	Yes
23	7·1	F	40	3150	None	Yes
24	17·0	M	38	3060	None	No
25*	13·7	M	40	3560	None	Yes
26*	12·4	F	37	3130	None	No
27*	6·1	M	43	3430	None	Yes
28*	15·0	M	40	3570	None	No
29*	7·5	M	40	3350	None	No

*Subjects 25–29 defaulted from follow up.
N/A, result not available; BPD, bronchopulmonary dysplasia; RDS, respiratory distress syndrome.

There is however, some evidence that inhaled steroids may be of value. Studies on the nebulised solutions have been disappointing, probably due to formulation problems.[13] This has been found particularly with beclomethasone suspension. It has been reported that less than 20% of the active drug is in particles less than 5 μm in diameter (a size likely to reach the smaller airways) when beclomethasone is nebulised using a standard device.[14] In order to overcome these problems, we have developed a face mask (Laerdal size 2) and spacer (Nebuhaler, Astra) metered dose inhaler delivery system.[15]

In this paper, we report the results of a double blind, crossover study investigating the effects of inhaled budesonide in wheezy infants who were less than 18 months of age.

Subjects

Twenty nine children aged 4 to 17 months (mean 11 months) were enrolled into the study (table 1). They had a history of recurrent cough and/or wheeze for greater than two months and for three or more days a week. They were each heard to wheeze on at least one occasion by a doctor. Specific conditions which could lead to recurrent respiratory symptoms, such as heart disease, cystic fibrosis, and gastro-oesophageal reflux, were excluded by clinical assessment and investigations as indicated.

Methods

The trial was a randomised, double blind, placebo controlled, crossover study, approved by the hospital's ethical committee. Children were referred for consideration for entry into the study by paediatricians at the Queen's Medical Centre, Nottingham, and at King's Mill Hospital, Mansfield. On referral parents were instructed to keep a symptom diary. The parameters of breathlessness, wheeze, and cough during the night and the day were given a score of between 0 and 3 on an arbitrary ordinal scale, 0 for no symptoms and 3 for severe symptoms. They were also asked to keep a record of the amount of bronchodilator treatment they administered to their child as they felt necessary. If a child wasn't receiving a bronchodilator at the time of referral, they were given an ipratropium bromide metered dose inhaler with a coffee cup spacer to use. On review three weeks later, if they met the criteria for inclusion into the study, written, informed parental consent was obtained. The children were randomised to one of two treatment sequences starting with either budesonide or placebo. They were then shown how to use the modified Nebuhaler (which has previously been described[15]) and asked to continue keeping a symptom diary.

Three puffs of budesonide equivalent to 150 µg, or three puffs of placebo were administered into the Nebuhaler with the valve closed. The Nebuhaler was then tipped downwards to open the valve by gravity and the mask was applied to the child's face to provide an airtight seal. The parents were asked to keep it in position for 10 to 20 seconds and on removal were instructed to wipe their child's face to remove excess aerosol. The treatment was given twice daily. If a child accepted the mask particularly poorly, the parents were instructed to administer the treatment in the same manner but when their child was asleep. If the child still would not accept the mask, this was regarded as intolerance of the device and the child was withdrawn from further participation in the study. Hospital review was undertaken every three weeks for a clinical assessment and retrieval of the current symptom diary and aerosol canister for weighing. A new diary and canister were then supplied. At six weeks the children were changed onto the opposite treatment.

Symptom scores and additional treatment data were analysed for the second three weeks of each six week treatment period. This was to allow for establishment of the treatment or a washout period during the first three weeks of each six week period. Symptom scores were analysed individually for each parameter and also summated to give a 24 hour total symptom score.

Children whose clinical condition deteriorated significantly, necessitating a breaking of the code, were to be regarded as treatment failures and withdrawn from further participation.

Finally, we asked the parents for their preference between the two treatments before the code was broken.

ANALYSIS

Symptom scores were analysed using the Mann-Whitney U test to compare the differences between those who started on placebo and those who started on budesonide. Parental preference was analysed by Fisher's exact test.

Results

Twenty nine children were enrolled into the study (table 1). Five defaulted from follow up before completion and resisted repeated requests to reattend. This left a study group of 24 children aged 4–17 months (mean 11 months) who could be assessed.

TOLERANCE

Twenty out of the 24 children (83%) were able to tolerate the modified Nebuhaler. Three (12·5%) would only do so while asleep. Four (17%) would not even tolerate the device while asleep and could proceed no further in the trial. They were withdrawn at the end of the first three week period.

There were two treatment failures, both of whom were on placebo at the time. One of these had an exacerbation of his symptoms with an upper respiratory infection and was prescribed oral steroids by his family doctor. He showed no response to the prednisolone or subsequently to budesonide. The other child relapsed in the final period with no precipitating factors apart from the change in treatment from budesonide to placebo. He made a good recovery on restarting budesonide. One child developed *Haemophilus influenzae* meningitis while receiving the placebo treatment, having not previously received budesonide. He was withdrawn when diagnosis of meningitis was made.

PREFERENCE

Eighteen sets of parents (including one of the two whose children were failures on placebo treatment, and who started but failed to complete the final three weeks), were in a position to express a preference at the end of the study. Eleven (61%) preferred budesonide to placebo, and one set preferred placebo (p=0·01). Five (28%) thought that neither treatment made a difference and one (5·5%) thought both treatments were effective. There was no significant treatment order effect (period effect, p=0·8; carry over effect, p=0·5).

SYMPTOMS

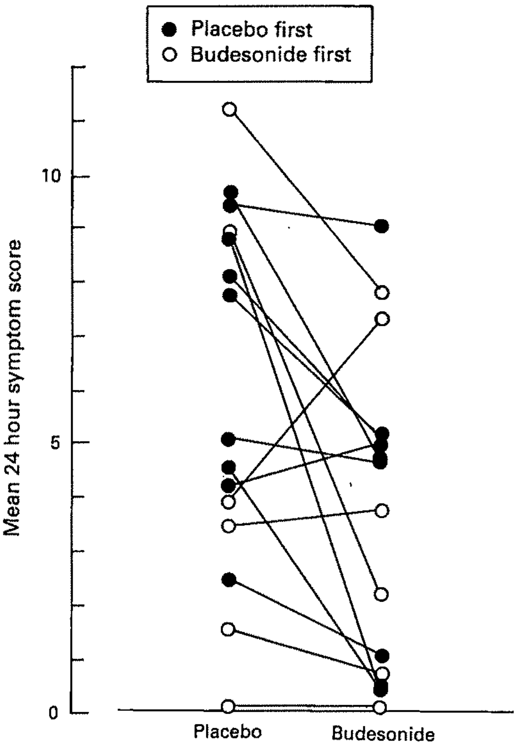
Fifteen children had diaries complete enough to be suitable for analysis. Individual trends are shown in the figure. The mean total 24 hour symptom score and the mean individual symptom score parameters were better on budesonide (table 2). All symptom scores apart from nocturnal wheeze and cough showed a significant difference. This effect was also apparently independent of treatment order (period effect, p=0·4; carry over effect, p=0·5).

Less rescue bronchodilator was used while on budesonide, but as children varied in which

Table 2 Symptom diary analysis

Score parameter	*Mean placebo −budesonide difference (95% confidence interval)*	*p Value*
Breathlessness		
Night	0·21 (0·05 to 0·37)	0·02
Day	0·29 (0·05 to 0·53)	0·02
Wheeze		
Night	0·38 (−0·06 to 0·82)	0·13
Day	0·53 (0·10 to 0·96)	0·03
Cough		
Night	0·35 (0·00 to 0·70)	0·07
Day	0·35 (0·05 to 0·65)	0·04
Total 24 hour symptom score *	2·1 (0·04 to 3·8)	0·03
24 hour treatment score	0·27 (−0·06 to 0·60)	0·12

*The power of this study to detect a symptom score difference of ±2 at the 95% significance level=0·26.



Symptom score according study phase for individual subjects.

bronchodilator they were given, this reduction was not significant (table 2).

There was no difference between the group who responded to treatment and those who did not in terms of family history of atopy. Three of the non-responders were ventilated in the newborn period. Two of these had respiratory distress syndrome and subsequent bronchopulmonary dysplasia, the other had pneumonia. One of those who responded had respiratory distress syndrome but was not ventilated.

Discussion

The use of a large volume spacer with attached face mask to administer aerosols to children was first suggested by Freigang as long ago as 1977.[16] Even though the same author and many others have documented the beneficial effects of steroid aerosols in preschool children,[17–19] few studies of their effects in infancy have been reported. We have shown that it can be effective in administering inhaled steroids to a group of young infants who may need prophylaxis for persistent symptoms, and for whom there is no established, reliable alternative treatment. Recent work in our department has shown that this method of administering inhaled steroids is particularly suited to infants' tidal volumes. The dose of budesonide inhaled per kilogram body weight from metered dose inhaler using a Nebuhaler and face mask is then considerably greater compared to the dose inhaled by an adult using a Nebuhaler. The dose thus delivered, should be sufficient to produce a response if the drug is appropriate to this age group.

Approximately half of our study group of 24 were treated successfully, comprising three quarters who could tolerate the modified Nebuhaler, two thirds of whom responded to the treatment given in this way. Although we found no statistically significant treatment order effects, it may be that the washout period of three weeks was not quite adequate, thus tending to minimise the recorded symptom score difference between budesonide and placebo when budesonide was administered first. This was suggested by the observation that the group who received budesonide first had a mean improvement in symptom scores about half that of the other group. In addition, two sets of parents in the 'budesonide first' group implied that they felt the placebo had some activity: one of these preferred placebo the other felt that both treatments helped. It may be that the effects of topical steroids persist for several months and would therefore still be present after only a three week washout.[20] Our treatment period of six weeks may have been too short to show the maximum effect of budesonide in all cases. In their study, Bisgaard and colleagues saw an improvement up to eight weeks after the onset of treatment before a plateau was reached. In the same study they showed inhaled budesonide to be effective when administered using a similar but more complicated adaptation of the Nebuhaler.[21] They used a higher dose in a slightly older group of children.[22] In a group of children of similar age to ours, however, Van Bever and colleagues were not able to demonstrate a significant improvement in symptoms using nebulised budesonide.[23]

The group of wheezy children in our study could not all necessarily be firmly classed as having asthma, and it was interesting to note the poor response of a subgroup of three children who had been ventilated in the newborn period. However, the small numbers involved make it impossible to draw any firm conclusions from this particular observation. In conclusion, for this age group of children in whom therapeutic options are limited, budesonide administered in this way offers a useful addition to the available range.

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Vitamin A again

One of the most exciting recent developments in paediatrics has been the realisation that giving supplements of vitamin A to young children in developing countries might prevent enormous numbers of deaths not only from measles (see Archivist 1991: 139) but from other causes.[1] It has been estimated that some 5–10 million children world wide develop xerophthalmia each year and between five and 10 times that number suffer from subclinical vitamin A deficiency, which leads to increased mortality from diarrhoeal and respiratory diseases. Trials of vitamin A supplementation in Indonesia[2] and India[3] have shown reductions in preschool child mortality of between a third and half, although another trial in India[4] produced negative results. Now another trial, this time from Nepal, has produced encouraging results (Keith P West Jr and colleagues, *Lancet* 1991; **338**: 67–71).

In all 28 630 children aged between 6 months and 5 years entered the trial. They lived in 261 wards in the rural plains district of Sarlahi and each ward was allocated at random to treatment or placebo, treatment consisting of vitamin A in a dose of 60 000 retinol equivalents (200 000 IU) for children of 12 months or more and half that for those less than 12 months, given every four months. Placebo consisted of vitamin A, 300 or 150 retinol equivalents according to age, also given every four months.

Over a 12 month period of follow up mortality was 16·4 per 1000 child years in the placebo group and 11·5 per 1000 child years in the vitamin A supplemented group. Supplementation, therefore, gave a 30% reduction in mortality or a protective relative risk of 0·7. The benefit was seen in both sexes, at all ages within the range studied, and throughout the year and it did not seem to be affected by the child's nutritional status. Significant reductions were seen for deaths attributed to measles (relative risk 0·24), non-specified infections (0·52), diarrhoea (0·61), and malnutrition (0·65) but, surprisingly, not for pneumonia.

It is estimated that vitamin A supplementation for preschool children might save over 15 000 lives in Nepal each year and about a million in the whole of south Asia.

ARCHIVIST

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Archives of Disease in Childhood 1992; **67**: 289–293

Bronchodilators for treatment of mild bronchiolitis: a factorial randomised trial

Elaine E L Wang, Ruth Milner, Upton Allen, Helen Maj

Abstract

A randomised double blind trial was conducted to determine the efficacy of inhaled bronchodilators, salbutamol and ipratropium bromide, compared with placebo in the treatment of bronchiolitis. Patients, who were 2 months to 2 years of age and without underlying cardiac or pulmonary disease, received drug 1 (salbutamol or saline placebo) followed one hour later by drug 2 (ipratropium bromide or placebo). Both agents were administered every four hours. The patients were allocated to one of four groups according to a factorial design. The four groups were similar in demographic characteristics, initial oxygenation, and clinical score. The change in oxygen saturation of recipients of both agents was significantly better than that of recipients of salbutamol alone or ipratropium bromide alone. This change, however, was not statistically different from that of the control group. No difference was observed in the clinical score or hospital duration. Inhaled bronchodilators did not improve the condition of hospitalised mild bronchiolitis.

Bronchiolitis is a major cause of morbidity in young infants. Because of similar clinical findings between bronchiolitis and asthma, and because half of all bronchiolitics go on to develop reversible airway disease, numerous investigators have examined the efficacy of bronchodilators in this patient population.[1–8] For the most part these studies did not find any benefit from bronchodilators. However, they have been criticised because patients needed to be sedated for the tests, which also resulted in the tests being performed during the convalescent rather than the acute phase of illness. More recently three double blind randomised studies conducted in the emergency room found bronchodilators to be effective as measured with a clinical score[9 10] or pulse oximetry and measures of respiratory rate and retractions.[11]

This study was conducted to examine the efficacy of inhaled bronchodilators in hospitalised patients using pulse oximetry and clinical score. Observer agreement for these measures had previously been assessed in a similar patient population.[12] There was very good agreement for assessments of pulse oximetry and moderate agreement for those of clinical assessment.

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Patients and methods

The study was carried out at the Hospital for Sick Children in Toronto, Canada. This 600 bed facility is the referral hospital for central and southern Ontario as well as the main paediatric hospital serving Toronto, a municipality of 2·5 million people. The usual practice for treatment of bronchiolitis in the emergency department at this hospital has been to administer two to three treatments of salbutamol by inhalation. Infants who 'respond' are discharged on a variety of oral medications, most commonly orciprenaline. Infants with an 'inadequate response' are admitted to hospital. Before commencement of the study over 90% of hospitalised patients were treated with inhaled salbutamol.

All patients aged 2 months to 2 years hospitalised for the first time with bronchiolitis were eligible for the study, except if they had known underlying cardiac or pulmonary disease, they had been transferred from another hospital, their condition was rapidly deteriorating, or the parents or attending physicians refused their participation in the study. Thus, all patients admitted into this study did not have adequate improvement with emergency department management which always included salbutamol. Bronchiolitis was diagnosed by the attending paediatrician on the ward in the presence of expiratory wheezing of acute onset accompanied by signs of viral illness such as coryza.[13 14] The study was approved by the human subjects review committee at the hospital.

Patients were stratified into two groups: those 6 months of age or less and those older than 6 months, because of previous observations of poorer prognosis in young infants.[15–17] Patients were then randomised into one of four groups in a factorial design. Patients all received drug 1, which consisted of salbutamol (Ventolin, Glaxo) or normal saline placebo, followed by drug 2, which was ipratropium bromide (Atrovent, Boehringer Ingelheim) or normal saline, one hour later. All treatments were administered over 15 to 20 minutes by face mask and Whisperjet nebuliser (Marquest Medical Products) driven by oxygen at a flow rate of 6–7 l/minute. Both drugs 1 and 2 were repeated every four hours for the duration of hospitalisation or three days whichever came first. One group received salbutamol at 0·15 mg/kg/dose (0·03 ml/kg/dose) in 2 ml of saline followed one hour later by 0·5 ml or 1 ml of saline placebo. A second received 0·03 ml/kg of saline in 2 ml of saline followed by either 125 μg (0·5 ml) of ipratropium bromide if less than 6 months or 250 μg (1 ml) of ipratropium bromide if older than 6 months. A third group received both salbutamol and ipratropium bromide in the doses indicated. The final group received saline placebos in the same volumes indicated. The contents of drug 1 and 2 were not indicated on the supplies sent to the ward and only the pharmacy staff were aware of the allocation until the code was broken at the conclusion of the study.

A nasopharyngeal swab was obtained from both nostrils for immunofluorescence assay for detection of respiratory syncytial virus, influenza, parainfluenza, and adenovirus antigens.[18] The same specimen was used for isolation of respiratory viruses and enteroviruses on green monkey kidney, Graham's 293, and Hep 2 cell lines.

Oxygen saturation was measured on admission and again on the later of two days: the discharge day or day 3 if the patient remained in hospital. The value was determined after monitoring children in an awake non-crying state for 10 minutes using pulse oximetry (Nellcor). Additionally, in order to avoid effects of bronchodilator, patients were assessed during the longer of the two intervals between bronchodilators, just before drug 1 was administered. In three patients, oxygen supplementation was discontinued 10 minutes before measurement of oxygen saturation. No other patients were receiving oxygen supplementation at the time of evaluation. The day 3 measurement was selected because it was the median length of stay of our patients with bronchiolitis. Patients were graded for severity with respect to respiratory rate, retractions, wheezing, and general condition (table 1) on admission and discharge or day 3. This score was adapted from one that has previously been used in studies of childhood reactive airway disease including bronchiolitis.[19] Patients were assessed by study personnel (EELW and HM) who were blinded to the treatment allocation on enrolment and on discharge or the third hospitalisation day if the patient was still in hospital. Interobserver agreement had previously been demonstrated for these investigators.[12] In addition, the research nurse (HM) visited daily and was informed of any untoward events.

Comparability between the four intervention groups was assessed using χ^2 analysis for proportions of Kruskal-Wallis analysis for enrolment oxygen saturation and clinical score, which were not normally distributed.

The primary outcome was the change in oxygen saturation and severity score between admission and day 3. For patients discharged before day 3, the discharge values were considered to be the same as day 3 values. A two way analysis of variance was used to determine the independent effects of salbutamol and ipratropium bromide as well as their interaction on the change scores and hospital duration.[20]

Results

Between 4 January 1988 and 30 June 1989, 342 patients were hospitalised with bronchiolitis. Of these, 192 were ineligible, 40 were missed when the study team were not called, and 48 were not enrolled because parents refused to consent to the study. Thus 62 infants were enrolled in the study.

Respiratory syncytial virus was identified by immunofluorescence or viral isolation from 16 of 60 patients (27%) in whom the virology laboratory received an adequate specimen. No other viral agents were recovered.

There was no difference between groups in the gender or age distribution, the frequency of family history of atopy, prior use of bronchodilators, or identification of a causative organism by χ^2 analysis ($p>0\cdot01$, table 2). However, relatively fewer boys appeared to have been randomised to receive placebo. Similarly, no difference in the enrolment oxygen saturation or clinical score was observed using Kruskal-Wallis analysis ($p>0\cdot10$).

A significant difference was observed within the four treatment groups for their effect on change in oxygenation ($F=8\cdot96$, $p=0\cdot004$; fig 1). The change in oximetry of the recipients of both salbutamol and ipratropium bromide was significantly better than in those receiving salbutamol alone ($F=10\cdot24$, $p=0\cdot002$) and ipratropium bromide alone ($F=4\cdot14$, $p=0\cdot04$). However, the mean change in oxygen saturation with both agents was not significantly different from that in the placebo control group ($F=0\cdot8$, $p>0\cdot1$). The poorer response with salbutamol

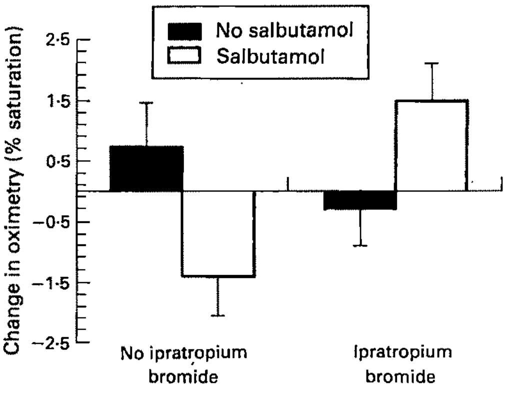

Figure 1 Change in oxygen saturation by treatment group. Results are mean (SE).

Table 1 Definition of categories for clinical assessment

	Score			
	0	*1*	*2*	*3*
Respiratory rate (breaths/min)	≤30	30–45	46–60	>60
Wheezing	None	Terminal expiration or only with stethoscope	Entire expiration or audible on expiration without stethoscope	Inspiration and expiration without stethoscope
Retractions	None	Intercostal only	Tracheosternal	Severe with nasal flow
General condition	Normal			Irritable/lethargic/poor feeding

Table 2 Comparability of groups for demographic characteristics, previous bronchodilator use, viral recovery, initial oxygen saturation, and clinical score

	Salbutamol and ipratropium bromide	*Salbutamol only*	*Ipratropium bromide only*	*Saline placebo*
Sex (M/F)	9/8	8/6	11/4	6/10
Age (months)				
≤6	8	6	6	6
>6	9	8	9	10
Family history of atopy				
Yes	7	4	7	8
No	10	10	8	7
Previous use of bronchodilators				
Yes	3	1	3	4
No	14	13	12	12
Causative organism				
Respiratory syncytial virus	5	4	4	3
None	12	9	11	12
Initial median oxygen saturation (%)	96	96·5	97	96·5
Range	86–99	94–100	93–100	92–100
Initial median clinical score	5	5	4	6
Range	2–9	0–8	1–6	3–11

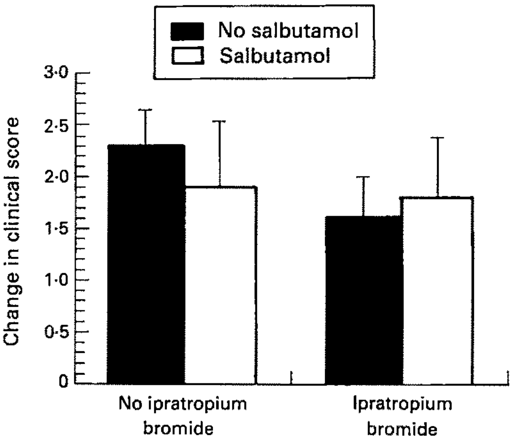

Figure 2 Change in clinical score by treatment group. Results are mean (SE).

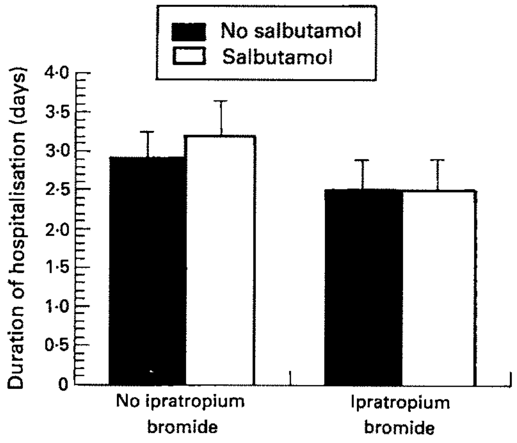

Figure 3 Duration of hospitalisation by treatment group. Results are mean (SE).

was also significant when compared with the control (F=4·81, p=0·03). No significant difference was observed for either agent or the combination on clinical score or hospitalisation compared with placebo (figs 2, 3). In fact, the mean clinical score improved the most in the placebo recipients (fig 2). The distribution of oxygen saturation change according to the day of final assessment is displayed in fig 4. Again, there was no significant difference among the study groups.

Four patients had worsening of their disease. Two patients had received both active agents: one was transferred to the intensive care unit for respiratory support after receiving the first dose of each medication and the other was placed on tribavirin (ribavirin) because of cyanosis and respiratory distress. A third patient, subsequently found to be in the control group, deteriorated after the first mask and was placed on continuous salbutamol. Finally, one patient who was allocated to the salbutamol alone group developed increasing respiratory distress and was started on systemic steroids and theophylline. One additional patient, receiving salbutamol only, was withdrawn after three days in the study because of tremulousness after the medication.

Discussion

There continues to be controversy about the use of bronchodilators in the management of bronchiolitis. A recent survey conducted of 21 paediatric allergists and pulmonologists indicated that the majority would use bronchodilators in bronchiolitis.[21] This occurred despite the fact that current textbooks do not recommend these agents for this condition.[22] Older studies measuring pulmonary function tests before and after bronchodilators observed no improvement with bronchodilators.[1–6 8 23] However, because of the necessity of sedation in order to obtain these measurements, the patients were not in the acute phase of their disease.[24] The validity of these pulmonary function tests have also been questioned.[25] One study in intubated patients has observed a 43% improvement in maximum expiratory flow rate suggesting that bronchodilator treatment is useful in the acute phase of disease.[26] Also, more recently studies conducted in the emergency room have concluded that inhaled salbutamol[10 11] and subcutaneous adrenaline[9] are efficacious at least in the short term in these settings. However, the number of return visits or admissions were not reported. One possible explanation for the contradictory result is that there are two clusters of patient responses. Soto and coworkers observed that 30% of their patient population had improved conductance after bronchodilators whereas the rest had not.[27]

Because of the usual practice at our study hospital, the patients who were enrolled in this study had mild bronchiolitis as demonstrated by their oxygen saturation and clinical score on admission. However, in this population of patients with mild disease, there was no benefit in using bronchodilators. When either agent was used alone, the oximetry actually decreased compared with admission values in contradistinction to the group that received both active agents and the control group. The benefit of combining these agents over using the agents singly has been shown in asthma and chronic obstructive pulmonary disease treatment.[28–30]

Tal and coworkers found improvement only

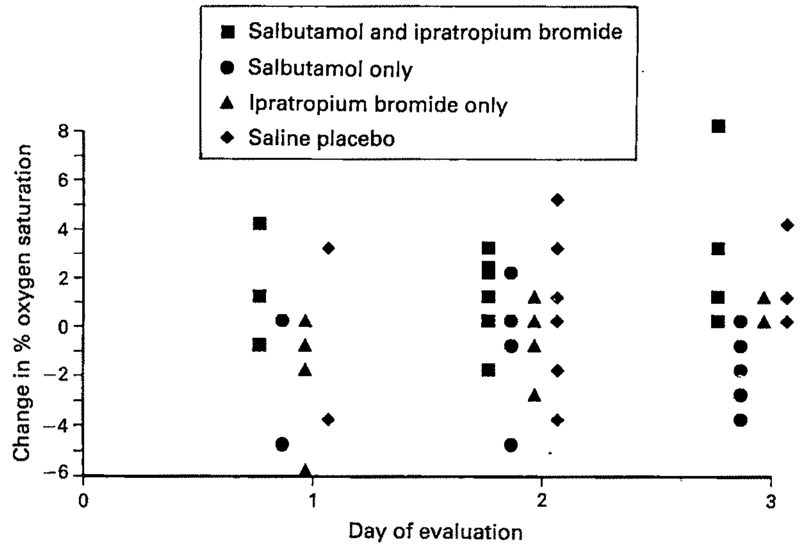

Figure 4 Change in % oxygen saturation according to day of final evaluation.

in infants treated with both salbutamol and dexamethasone.[7] However, average daily clinical scores, arterial carbon dioxide and oxygen tensions, and duration of hospitalisation were not significantly different for the salbutamol group compared with those not receiving salbutamol. Stokes *et al* observed an improvement in work of breathing with ipratropium bromide but not with salbutamol.[5] This caused Henry and coworkers to study the clinical efficacy of ipratropium bromide compared with saline placebo in 66 infants as determined by parental and nursing staff assessments.[1] The daily improvement in clinical score suggested to the authors that the measurements were sensitive to change. The number of treatments required were similar between the two groups. No benefit from ipratropium bromide was observed in this study.

The difference in our conclusions compared with studies conducted in emergency department settings[9–11] may be because the study outcomes were taken days after hospitalisation. The objective of the study was to determine whether there would be an effect of the drugs on improving the condition of hospitalised children with possible reduction in hospital stay rather than the short term effect of these agents as seen in the emergency room. Furthermore, our study population consisted of those patients who failed to show an adequate improvement to allow them to be discharged from the emergency department. It is possible that those patients with bronchiolitis who respond to bronchodilators are not hospitalised.

Although the small study size may have limited the power to detect differences, the negative effect of salbutamol on oximetry measurement and the small magnitude of the differences observed in the study makes it highly unlikely that bronchodilators are effective in the patient population studied.

Of concern was the observation of untoward effects in patients in this study. The study was not designed to have adequate power to detect differences in complication rates such as requirement for ventilatory support or tribavirin because of their infrequent occurrence. However, our data do not suggest that these agents can prevent these serious events. In addition, one of the younger infants developed severe enough tremulousness to warrant discontinuation of salbutamol by the attending physician, suggesting that bronchodilators are not totally benign agents. This observation and the decline in pulmonary function with salbutamol observed in ours and previous studies[4 31] emphasises the need for caution in prescribing bronchodilators for this illness.

We did not find that bronchodilators improved oxygen saturation or clinical score enough to result in shorter hospitalisation in patients with mild bronchiolitis. Decisions on using these agents must be based on their short term benefit which, although statistically significant, amounted to a mean improvement of only 2% in oxygen saturation.[11] The use of either salbutamol or ipratropium bromide in the treatment of patients hospitalised with mild bronchiolitis cannot be recommended.

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AIDS in Romania

One of the most emotionally draining pieces of writing, fact or fiction, I have ever read is the article about AIDS in Romania published in the *Lancet* on 14 September (Bradley S Hersh and colleagues, *Lancet* 1991;**338**:645–9). As a testament to the depths of the pit which human beings are capable of digging for themselves it can have had few equals since the writings of George Orwell and Aldous Huxley and the more graphic accounts of the holocaust or the killing fields of Cambodia. Not that the article is written in anything other than proper, factual, scientific style; it isn't, but the facts themselves are harrowing.

Romania is a country of 23 million people. In the year after the death of Ceaucescu 1168 cases of AIDS were reported to the Ministry of Health and 94% of those were children under 13 years, almost all (99%) less than 4 years old. Nearly two thirds of them had been abandoned by their parents and were living in public institutions. How did they get AIDS? Not, it seems, from their mothers, for only 8% of tested mothers were HIV positive. A very small number (0·5%) of the children had received blood products for clotting disorders but 39% of them had been given transfusions of unscreened blood. Most (57%) of them appear to have got the disease through the repeated use of inadequately sterilised needles and syringes in their orphanages and 'dystrophic centres'. At the time of the demise of the regime there were 14 000 children less than 4 years old in orphanages and 2500 chronically ill or malnourished children in those revoltingly named centres. A serological survey of 12 231 children showed that 10% were HIV positive. In the orphanages it was 8% and in the centres 22%. In one district nearly half of the children in the institutions were HIV positive.

Why? Why did parents abandon their children? Were the parents themselves victims of the regime or had they simply been indoctrinated to believe that the responsibility was not theirs but the state's and that the state would provide? I am reminded of an incident on my own unit when a young couple were asked by a nurse if they would like to feed their baby and replied, 'No, that's your job' and went for a walk round the hospital grounds while it was done. A relatively minor incident and not to be compared with the much larger canvas, but what do we know about the infectivity of depravity? How is it that one apparently depraved monster can infect society with his own depravity?

It's possible to wax philosophical at some length about these things. I shall resist the temptation. But why? Why, why, why, why . . . ?

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The intensive care unit in paediatric oncology

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Abstract

There were 70 admissions from a regional paediatric oncology centre to the intensive care unit over a six and a half year period. Patients were divided into those with systemic infections (n=19), respiratory infections (n=15), metabolic effects (n=9), tumour mass effects (n=10), neurological complications (n=8), and others (n=9). The overall survival was 51%. Patients admitted with metabolic or tumour mass related effects had the best prognosis with a survival of 84%. If dialysis is required in this group of patients then continuous arteriovenous haemofiltration is recommended. Patients with systemic or respiratory infections comprised the main poor prognosis group with a survival of 26%. For patients with a systemic infection who required ventilation, the mortality was 100%. The outlook for patients with a generalised encephalopathy was also poor, with no neurologically intact survivors. The median APACHE-II (acute physiology and chronic health evaluation) score for patients who died was 27 and for survivors was 16. There is a need for close cooperation between staff of intensive care and paediatric oncology units. Alternative treatments should be considered for patients with systemic infections who require ventilation.

Over the past 15 years, with the introduction of increasingly intensive protocols, the nature of paediatric oncology has changed significantly. This has been accompanied by improved survival figures for children with both haematological and solid malignancies. It has, however, resulted in children spending extended periods in hospital with severe and life threatening complications of their malignancy and/or the associated treatment. Close cooperation with an intensive care facility is therefore an essential part of any regional oncology centre. Admission to an intensive care unit has many costs that include emotional and social factors, as well as those that are medical and financial in nature. An understanding of the benefits of an intensive care unit is therefore important for decision making and for counselling of the families involved. It was for these reasons that we undertook the present study.

Patients and methods

This study was performed over a six and a half year period, from July 1984 to December 1990. Details were recorded of all patients from the paediatric oncology unit at St James's University Hospital, Leeds, who required admission to the intensive care unit (ICU). The information used in this study was collected contemporaneously by the ICU, and was then clarified by retrospective chart review. There were a total of 65 patients admitted on 70 occasions in the study. Their underlying oncological diagnoses are given in table 1. Their mean age was 6·6 years (range 2 months–14·5 years), and there were 39 boys and 26 girls.

The paediatric oncology unit is a regional unit, serving Yorkshire and Humberside. There are on average 100 new patients presenting with primary malignancies each year. The only patients not included in this study were those requiring specialised neurosurgery, who were operated on at two nearby, regional neurology centres. However, many received subsequent medical treatment at St James's University Hospital.

The ICU is a combined adult and paediatric unit. Admission to the ICU is restricted by bed availability, and our oncology ward is capable of functioning as a high dependency unit. The nursing staff on the oncology ward have not received an intensive care training but frequently care for acutely ill children. Patients are admitted to the ICU when they require respiratory support, cardiovascular support, or complex monitoring. We have standard policies on our ward for the treatment of febrile neutropenia and for patients presenting with tumour lysis syndrome and airway obstruction.

All febrile neutropenic patients receive early treatment with broad spectrum antibiotics, with haematological support where necessary. If signs of endotoxic shock are present with hypotension, tachycardia, poor peripheral circulation, and reduced urine output then plasma expanders are used. If a rapid response is not obtained inotropic agents are given, initially as low dose dopamine. Providing patients are stable, with restitution of blood pressure, improved circulation, and increased urine output they will continue to be treated on

Table 1 Survival by oncological diagnosis

Diagnosis	*No of cases*	*No (%) surviving*
Acute lymphoblastic leukaemia	30	12 (40)
Acute myeloid luekaemia	9	5 (56)
Non-Hodgkin's lymphoma	13	9 (69)
Hodgkin's lymphoma	1	1
Juvenile chronic granulocytic leukaemia	2	0
Histiocytosis	2	0
Solid tumours	13	9 (69)
Total	70	36 (51)

the ward. Transfer to the ICU is sought if a response is not obtained and/or double inotropic support (dopamine/dobutamine) is required.

Patients with the potential for developing tumour lysis syndrome are treated on the ward with allopurinol, hydration, and alkalinisation of their urine. Chemotherapy is withheld until their metabolic status has been stabilised. Patients are transferred to the ICU when indicated or if deterioration is anticipated.

The APACHE-II (acute physiology and chronic health evaluation) severity of disease score was assessed by the ICU staff on the basis of the first 24 hours after admission.[1] The difference between medians was calculated using the Mann-Whitney U test. The other information collected prospectively included age, sex, date of admission and discharge, reason for admission, treatment delivered in the ICU and the outcome. Patients with a successful outcome were defined as those who were alive one week after leaving the ICU. Duration of stay in the ICU was calculated as a whole day providing the patient was in the ICU for greater than 12 hours of that day. If the patient was in the ICU for more than one day, the day of discharge was not included in the duration of stay calculation.

Results

Over the six and a half years there were 70 paediatric oncology admissions to the ICU. The overall survival was 51%. Survival by oncological diagnosis is shown in table 1. Of the 13 patients with non-Hodgkin's lymphoma nine were admitted for metabolic and/or tumour effects. Survival was 89% for these nine patients. Survival for children with acute lymphoblastic leukaemia (ALL) was the lowest, being 40%, but this diagnostic group contained the highest proportion of infected patients (67%).

Survival by reason for admission to the ICU is shown in table 2. A number of patients had multiple pathologies. However, they were allocated to a group by their most important or dominant pathology.

SYSTEMIC INFECTIONS

The largest group consisted of 19 patients with systemic infections. Twelve of these patients had a Gram negative septicaemia with the following organisms cultured: *Escherichia coli* in six, *Pseudomonas aeruginosa* in three, *Klebsiella* spp in two and *Bacteroides fragilis* in one. A single patient had a possible Gram positive infection with enterobacter isolated, although its significance is unclear as it was only isolated in the mid-course of the illness. There were two systemic viral infections with herpes zoster and herpes simplex. There were three systemic fungal infections, with disseminated aspergillus in two and disseminated candidiasis in one. There was one patient in whom no organism was isolated.

The patients with Gram negative infections all presented with endotoxic shock unresponsive to initial management. In all cases they received intravenous antibiotics to which the organism was sensitive but continued to deteriorate clinically. All 12 received inotropic support with combined dopamine and dobutamine, and two required renal dialysis. Nine of the 12 patients were ventilated and all nine died. One of the ventilated patients developed adult respiratory distress syndrome (ARDS), becoming ventilator dependent and dying of respiratory failure. Three patients with Gram negative infections were not ventilated, and survived. No single indication for ventilation was used. Rather, ventilation was instituted on the basis of a combination of deranged blood gases, increased respiratory rate, clinical exhaustion, and altered level of consciousness.

The seven patients with other systemic, non-bacterial infections all required ventilation and subsequently died due to the primary infection. Six of these patients required inotropic support and three were dialysed. Invasive monitoring used for all patients with systemic or respiratory infections included both arterial access and central venous catheters. Pulmonary arterial catheters were not used. There was no additional serious morbidity related to the monitoring.

RESPIRATORY INFECTIONS

There were 15 patients with respiratory infections. The largest group were fungal, with six aspergillus and one candida infection. There were three viral infections with *Varicella zoster*, parainfluenzae, and giant cell pneumonitis. Three patients had presumed pneumocystis pneumonia with typical clinical and radiological features. In two patients there was no clear aetiology. The overall mortality for this group was 60%, being higher for the ventilated patients (73%). Six patients in this group required inotropic support and all six died.

Table 2 Survival by reason for admission. Results are number or number (%)

Reason for admission	No of patients	Invasive monitoring	Inotropes	Renal dialysis	Survival	
					Ventilated	Not ventilated
Systemic infection	19	19 (100)	18	5	0/16 (0)	3/3 (100)
Respiratory infection	15	15 (100)	6	0	3/11 (27)	3/4 (75)
Metabolic effect	9	7 (78)	0	3	3/5 (60)	4/4 (100)
Tumour mass effect	10	9 (90)	0	0	3/4 (75)	6/6 (100)
Neurological	8	6 (75)	0	0	3/5 (60)	2/3 (67)
Postoperative	5	3 (60)	0	0	2/3 (67)	2/2 (100)
Postcardiac arrest	2	2	1	0	0/2 (0)	—
Gastrointestinal bleed	1	1	0	0	—	1/1
Cardiac faiure	1	1	1	0	—	1/1
Total	70	63 (90)	26	8	14/46 (30)	22/24 (92)

METABOLIC EFFECTS

Details of patients presenting with metabolic effects are shown in table 3. Two of the patients required dialysis for tumour lysis syndrome with progressive hyperphosphataemia, hypocalcaemia, and reduced urine output. Both were treated with continuous arteriovenous haemofiltration which provided satisfactory metabolic and fluid control. Two patients developed symptomatic hyperkalaemia resulting in a cardiac arrest. Although one patient was resuscitated he remained severely neurologically handicapped and subsequently died of progressive disease.

IMPAIRED VENTILATION DUE TO TUMOUR MASS EFFECTS

Ten patients were admitted with impaired ventilation due to tumour mass effects (table 4), and included those with airway obstruction, and respiratory or cardiovascular compromise secondary to their tumour. Only one out of the 10 patients died. The overall survival for patients admitted to the ICU with metabolic or ventilation related tumour problems was 84%.

NEUROLOGICAL EFFECTS

Eight patients were admitted with primarily neurological disease (table 5). Only two patients survived neurologically intact and in both the disease was localised and reversible. The outlook for patients with generalised encephalopathy was poor.

OTHERS

Two patients were admitted after a cardiac arrest on the ward. Only one survived, but he remained severely neurologically handicapped and died of progressive disease. The remaining details are shown in table 2.

Table 3 Metabolic effects

No	*Diagnosis*	*Reason for admission*	*Dialysis*	*Ventilation*	*Outcome*
1	NHL	Tumour lysis syndrome, incipient ARF	Yes	No	Survived
2	NHL	Tumour lysis syndrome, incipient ARF	Yes	No	Survived
3	NHL	Tumour lysis syndrome, incipient ARF	No	No	Survived
4	NHL	Tumour lysis syndrome, hyperkalaemia, cardiac arrest	No	Yes	Survived with severe neurological handicap
5	ALL	Tumour lysis syndrome hyperkalaemia	No	Yes	Died
6	ALL	High white cell count, anaemia (haemoglobin 2 g/l), acidosis (pH 6·7)	No	Yes	Survived
7	Malignant fibrous histiocytoma	Ifosfamide induced acute Fanconi's syndrome, acidosis	No	Yes	Survived
8	Wilms' tumour	Actinomycin induced, hepatorenal failure	Yes	Yes	Died
9	Hepatoblastoma	Adriamycin induced gastrointestinal toxicity	No	No	Survived

NHL, non-Hodgkin's lymphoma; ALL, acute lymphoblastic leukaemia; ARF, acute renal failure.

Table 4 Tumour effects with impaired ventilation

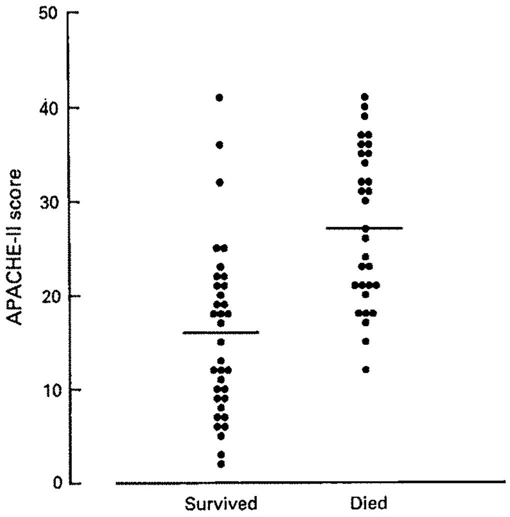
No	*Diagnosis*	*Reason for admission*	*Ventilated*	*Outcome*
1	NHL	Mediastinal compression, airway obstruction	Yes	Survived
2	NHL	Pleural effusion pulmonary oedema	Yes	Survived
3	NHL	Mediastinal compression, tumour invading heart, cardiac arrest	Yes	Died
4	NHL	Upper airway obstruction	No	Survived
5	NHL	Mediastinal compression	No	Survived
6	ALL	Mediastinal compression, airway obstruction	No	Survived
7	ALL	Mediastinal compression, pleural effusion, airway obstruction	No	Survived
8	Neuroblastoma	Abdominal mass, diaphragmatic splinting	Yes	Survived
9	Neuroblastoma	Abdominal mass, diaphragmatic splinting	No	Survived
10	Rhabdomyosarcoma	Abdominal mass, diaphragmatic splinting	No	Survived

NHL, non-Hodgkin's lymphoma; ALL, acute lymphoblastic leukaemia.

Table 5 Neurological disease

No	*Diagnosis*	*Reason for admission*	*Ventilation*	*Outcome*
1	Neuroblastoma	Cord compression, convulsions	Yes	Survived neurologically intact
2	ALL	Central nervous system deposits,	No	Survived neurologically intact
3	ALL	Radiotherapy related ascending myelitis	Yes	Survived with severe neurological handicap
4	ALL	Herpes encephalitis	Yes	Survived with severe neurological handicap, died of relapsed disease
5	ALL	Encephalopathy ? drug induced	No	Survived with severe neurological handicap
6	ALL	Encephalopathy	No	Died
7	AML	Intracerebral bleed	Yes	Died
8	PNET	Intracerebral bleed	Yes	Died

ALL, acute lymphoblastic leukaemia; AML, acute myeloblastic leukaemia; PNET, primitive neuroectodermal tumour.



APACHE-II severity of disease score. The horizontal line is the median value.

The APACHE-II severity of illness scores, evaluated over the first 24 hours, are shown in the figure. The median score for those who survived was 16 and for those who died was 27. The 95% confidence interval for difference between medians was 7 to 16 ($p<0{\cdot}001$). The three patients with APACHE-II scores greater than 30 who survived included a patient with ALL with tumour and metabolic effects; a patient with ALL with acute renal failure and a respiratory infection; and a patient with acute myeloblastic leukaemia (AML) who suffered hypoxia after general anaesthesia.

For all patients, the mean duration of stay in the ICU was 6 days, with a range of 1 to 56 days.

Discussion

This report documents our experience in the use of an intensive care unit by a regional paediatric oncology centre. There are few studies in the literature examining the role of an intensive care unit in this setting. Most are applicable only to adult oncology units, and there is a large variation in results and the conclusions drawn from these studies.[2–5] The only similar paediatric report comes from a combined study of three hospitals in Australia and Canada.[6]

The overall survival for all children in this study was 51%. The mortality was higher for those children who required ventilation, where there was only a 30% survival. Of those patients not ventilated two subsequently died. For both, an elective decision was made, after admission to the ICU, not to continue with active treatment because of progressive disease. All the remaining patients, who were not ventilated, survived.

The mortality, for patients admitted with a systemic infection, was 84% (16/19). Three patients who did not require ventilation were the only survivors. For those patients with a systemic infection who required ventilation, the mortality was therefore 100%. Febrile neutropenia is a common indication for admission to our oncology ward. We have an aggressive management policy for these patients, and the overall survival is in the order of 98%.[7] Patients are treated early with broad spectrum antibiotics and receive haematological and cardiovascular support when necessary. The septicaemic patients admitted to the ICU in our study therefore represent those patients where initial intensive therapy had failed and in whom cardiovascular and/or ventilatory support was required.

The majority of febrile neutropenic patients in whom a bacteraemia is diagnosed have a Gram positive infection.[7] There were no deaths due to proved Gram positive infections during this period, confirming the low mortality, although high morbidity, associated with these infections. By contrast, Gram negative infections, although fewer in number, remain difficult to control and are associated with a significant mortality.

We are concerned that all ventilated septicaemic patients died. Our experience is similar to that described by Butt *et al* who also reported a high mortality for these patients.[6] We reviewed in detail the case notes of the septicaemic patients in an attempt to identify factors that may have contributed to the patients' deaths. Factors examined included the time from the onset of marked cardiovascular symptoms to the use of inotropes, the subsequent time to admission to the ICU and to intubation, the indications for intubation, and the time the patient died. There were no common patterns. In four patients a possible factor may have been the delayed use of inotropes which were given more than 24 hours after the onset of marked cardiovascular symptoms, and it is now our practice to use inotropes earlier in the course of the disease. The early use of volume replacement together with low dose dopamine is therefore instituted on the oncology ward in appropriate patients. Admission to the ICU is then considered if the patient's condition remains unstable or if increased inotropic doses or double inotropic agents are required. If the prognosis is to be improved then alternative strategies need to be considered. It is in this group of patients that new therapies such as antiendotoxin antibodies should be evaluated.[8]

The best prognosis was seen in those children admitted with metabolic or tumour related effects. Although some of these children had high APACHE-II scores, their short term outlook is good provided their acute complications can be resolved. Patients with non-Hodgkin's lymphoma or acute lymphoblastic leukaemia presenting with a large mediastinal or abdominal mass are at risk for both tumour lysis syndrome and compression of airways or vital organs.

The true extent of airway obstruction may be difficult to assess and may be missed on anteroposterior chest radiographs. A penetrated lateral radiograph is recommended.[9] Clinical signs may also be misleading and obstruction may develop suddenly and without warning. General anaesthesia for diagnostic procedures is an important risk factor, with obstruction often presenting for the first time after the anaesthetic.[10] If general anaesthesia is required it should be performed by an anaesthetist skilled in the management of airway problems in children.

Tumour lysis syndrome is usually precipitated by cytotoxic chemotherapy, but can occur before treatment starts due to spontaneous lysing of lymphoblasts. Cytotoxic chemotherapy should preferably not be instituted until the patient's metabolic parameters have been stabilised. There has been increased recognition of the importance of hyperphosphataemia as a cause of acute renal failure, with lymphoblasts containing four times more phosphate than mature lymphocytes. Calcium phosphate crystals may be precipitated, resulting in renal tissue damage, renal tubular obstruction and metastatic calcification. Hypocalcaemia is an invariable consequence which may itself be symptomatic. The incidence of hyperkalaemia has been low in recently reported series due to improved fluid and acid-base management.[11] Nevertheless, hyperkalaemia remains potentially the most lethal complication with rapid rises in plasma potassium resulting in sudden death.

If standard conservative management fails to control metabolic parameters, then patients should be considered for early institution of renal dialysis. Although haemodialysis permits the correction of plasma electrolyte concentrations, there is still the possibility of large swings in plasma levels between treatments. In acutely ill patients there is also the potential complication of the disequilibrium syndrome and haemodynamic compromise. We therefore recommend the use of continuous arteriovenous haemofiltration (CAVH),[12] or haemodiafiltration if clearance is inadequate. CAVH was used to treat patients numbers 2 and 3 (table 3); it allows for the removal of large fluid volumes facilitating the concomitant administration of obligatory intravenous fluids. It is also haemodynamically gentle and provides a steady and continuous correction of metabolic parameters. Our ICU has since used venovenous haemofiltration which has fewer problems related to clotting of the filter.

The APACHE-II severity of disease classification, or similar scoring system, is widely used in many intensive care units. We acknowledge that the APACHE-II was not designed for children and that other systems such as the Admission Physiological Stability Index or the Organ System Failure Score are more appropriate.[13] Nevertheless the APACHE-II will still be used in many combined paediatric and adult units. Although patients who died had a significantly higher median APACHE-II score on admission, there was a large overlap. The APACHE-II score alone could not be used to predict the outcome for individual patients.

The decision to admit patients to the ICU is a complex process. Although the clinical status of the patient is the predominating factor, it is strongly influenced by the availability of intensive care beds as well as the capabilities of staff on the oncology unit and psychological pressures imposed by parents and staff. Patients whose condition requires ventilation or patients receiving double inotropes would form an absolute indication for admission to the ICU. More difficult questions arise where there is an increased need for monitoring and support without initial ventilation. Ideally we have tried to adopt a policy whereby, if early supportive measures fail, we initiate discussion with our intensivists. Within this study we are not aware of any children who were not admitted to our ICU if they fulfilled the above criteria. However, with the increased demand on ICU space and the greater intensity of paediatric oncology schedules, this becomes more of a possibility. Corresponding demands are placed on the oncology ward for the care of these acutely ill children.

Youngner *et al* have highlighted problems in attitude and misunderstanding which may exist between an oncology unit and the ICU, with resulting communication breakdown.[14] In order to offer the possibility of survival using modern intensive care techniques, it is essential to develop close working relationships between paediatric oncology and intensive care teams. This will allow for flexibility in decision making, providing sympathetic care that is in the best interest of the patients and their families. In addition, high risk groups, such as patients with Gram negative infections requiring ventilation, can be identified and new approaches evaluated.

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Pulse oximetry reference values at high altitude

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Abstract

Pulse oximetry is becoming popular for measuring oxygen saturation of haemoglobin in paediatric patients. There are no reference values for children living at high altitudes, and the aim of this study was to determine the values of oxygen saturation of haemoglobin in healthy children in Bogota (2640 m above sea level).

The saturation was determined in 189 children aged 5 days to 24 months with a Nellcor N10 oximeter. Mean values and 95% confidence intervals (CI) were calculated. Analysis of variance was used for assessing the differences in saturation with age and physiological status. The values were normally distributed with a mean (SD) of 93·3 (2·05)% and 95% CI of 93·0% to 93·6%. There were no clinically important differences in the oxygen saturation of haemoglobin in the range of ages included. The mean saturation in sleeping children was significantly lower than that during other physiological states (91·1% *v* 93·3%) but the difference was not clinically important.

As expected, the values for the oxygen saturation of haemoglobin in the children studied were lower than those reported from children living at sea level. These estimates can be used for interpreting results of the oxygen saturation in haemoglobin in children from Bogota and other cities located at a similar altitude.

Pulse oximetry is a method for continuous monitoring of the oxygen saturation of haemoglobin. The studies of validation of this method performed to date in paediatric patients have compared the results of the oxygen saturation of haemoglobin with the oxyhemoglobin saturation of arterial blood (SaO_2) and with the transcutaneous pressure of oxygen. These reports have shown correlation coefficient values between 0·86 and 0·99, and mean differences between oxygen saturation of haemoglobin and SaO_2 in the range from +0·2% to +2·9%.[1–7] All these studies confirm a strong correlation between the oxygen saturation of haemoglobin and other techniques of measuring the SaO_2. One additional study, which included subjects with severe hypoxaemia, suggests that pulse oximetry can be less precise when oxygen saturation of haemoglobin is below 65%.[8] Pulse oximetry has been reliable for monitoring purposes in subjects of all ages during anaesthesia and in intensive care units, providing accurate data.[1 9 10]

To our knowledge there are no previous reports of reference values for this technique in children living at high altitude. The goal of this study was to determine the values of the oxygen saturation of haemoglobin measured by pulse oximetry in a sample of normal children living in the city of Bogota (2640 m above sea level).

Subjects and methods

A descriptive observational study was conducted. During the months of January to March of 1990 we studied a group of 190 clinically healthy children aged 5 days to 24 months inclusive, born and permanently residing in the city of Bogota. The subjects were selected from the outpatient departments of the San Ignacio's University Hospital and the Colsubsidio Children's Hospital. These two hospitals are tertiary referral centres that also provide primary care for ambulatory patients. Children were excluded from the study because of: (1) any respiratory symptom in the two weeks before the examination. (2) Any abnormal sign on respiratory and/or cardiovascular clinical examination. (3) A history of chronical pulmonary or cardiovascular disease. (4) A history of neonatal respiratory illness. (5) Blood transfusions during the previous six months. (6) Malnutrition (height to weight relation below fifth centile on the National Center for Health Statistics tables). One of the subjects was later excluded because after reviewing his data the relation of height to weight was below that required for participation. Table 1 summarises the main demographic characteristics of the children studied. The study protocol was approved by the research committees of both health centres. Informed consent was obtained from parents before including any patient.

All measurements were done with a Nellcor N10 oximeter by one of the researchers (ORD). To determine the oxygen saturation of haemoglobin an adhesive sensor was placed on the

Table 1 Distribution of subjects according to age and sex

	No (%)
Age (months):	
<1	39 (20·6)
1–3	35 (18·5)
4–6	24 (12·7)
7–12	23 (12·2)
13–18	38 (20·1)
19–24	30 (15·9)
Total	189 (100)
Sex:	
Male	98 (51·9)
Female	91 (48·1)

index finger on the hand of the subject. The oximeter was set on normal mode. A measurement was considered successful when the oximeter displayed the subject's cardiac rate, which requires a reading by the machine of at least 10 seconds. The oximeter pulse amplitude indicator displayed on the screen was compared with the simultaneous measurement of the radial pulse obtained by palpation in the other hand to be sure that signals were coincident. If the sensor was not able to track the pulse during the measurement period due to excessive patient motion, no saturation reading was obtained and a check sensor signal was displayed. In these cases the measurement was repeated until the oxygen saturation of haemoglobin was obtained. All readings were duplicated and were taken if possible with the child awake and resting. When this was not possible, measurement conditions (crying, sleeping, or feeding) were noted. When exposed to a source of bright light (for example during phototherapy) the sensor was covered or the source of light was temporarily turned off. In order to demonstrate that the pulse oximeter was functioning properly, simultaneous measurements of oxygen saturation of haemoglobin and SaO_2 were performed in a group of 11 patients admitted to the intensive care unit. Blood samples obtained by arterial puncture were processed on a Hemoximeter OSM2 co-oximeter (Radiometer). The concordance between the oxygen saturation of haemoglobin and SaO_2 was very high, with an intraclass correlation coefficient of 0·98.

As the data had a normal distribution, means and 95% confidence intervals (CI) were calculated for all age and clinical status groups and compared by analysis of variance. The concordance between our oximeter and arterial blood saturation readings was assessed calculating the intraclass correlation coefficient.[11]

Results

As the data for the oxygen saturation of haemoglobin were distributed on an unimodal and symmetric fashion, mean (SD) values were calculated. The lowest and highest values were 84% and 100%, respectively, with a mean (SD) of 93·3 (2·05)% (median=93·0, mode=93·0). The 95% CI for the mean oxygen saturation of haemoglobin was 93·0% to 93·6%. Mean values and 95% CI for the different age groups were also calculated and are summarised in table 2. The mean value for oxygen saturation of haemoglobin in children aged less than 1 month was statistically different from that in the group who were between 13 and 18 months of age (92·6% and 93·7%, respectively; $p<0·05$, one way analysis of variance).

Table 2 Mean (%) value for the oxygen saturation of haemoglobin in different age groups

Age (months)	*Mean (%)*	*95% CI*
<1	92·6	92·1 to 93·2*
1–3	93·5	92·6 to 94·4
4–6	93·5	92·6 to 94·4
7–12	93·4	92·4 to 94·4
13–18	93·7	93·2 to 94·3*
19–24	93·0	92·3 to 93·7
Total	93·3	93·0 to 93·6

*<1 month *v* 13–18 months, $p<0·05$ by analysis of variance.

Table 3 Mean (%) value for the oxygen saturation of haemoglobin in different physiological states

State	*No of infants*	*Mean (%)*
Quiet wakefulness	150	93·4
Sleeping	8	91·1*
Crying	15	93·3
Sucking	16	93·5
Total	189	93·3

*$p<0·05$ by analysis of variance.

Table 3 presents the distribution depending on the physiological state of the child when conducting the measurements, as well as the mean value for oxygen saturation of haemoglobin in each group. Most of the readings were done with the subject alert and resting. A few measurements were obtained with the child crying, sleeping, or sucking. The mean value of the oxygen saturation of haemoglobin in the group of children sleeping was slightly lower (91·1% and between 93·3% and 93·5% for sleeping and other states, respectively). This difference was statistically significant ($p<0·05$, one way anaysis of variance).

Discussion

Up to the present two published studies have evaluated the values of the oxygen saturation of haemoglobin in both preterm and term healthy newborns, as well as in infants up to 6 months of age.[12] [13] These two studies were conducted in the Hospital for Sick Children in Toronto, Canada, a city that is less than 100 m above sea level. As individuals living at high altitude are in a hypobaric state, their normal oxygen tension and SaO_2 values may be different to those from individuals who live at lower altitudes.[14] To date, there have been no reports of reference values for oxygen saturation in haemoglobin in the paediatric population living at high altitude. These reference values will be helpful both in clinical practice and in research. As was expected by the lower barometric pressure of Bogota, the mean value for the oxygen saturation of haemoglobin obtained in our study is below that reported in healthy children in Toronto (93·3% and 96·4% respectively).[12] The lowest value observed in our sample was 84% and was obtained from a sleeping 2 month old infant. The highest value was 100% observed in a 10 month old crying child. It is not likely that these extreme readings were due to an oximeter dysfunction, because these data were confirmed on three different readings. These extreme values are uncommon in healthy children residing in Bogota.

As the main goal of our study was to obtain the values for oxygen saturation of haemoglobin on healthy children, it was necessary to select the study subjects carefully. The criteria used to select the sample were rigorous. None of the children included suffered from serious diseases, particularly acute or chronic cardiopulmonary illnesses. The data presented in table 1 show that an adequate representation of both sexes and of all ages in the two first years of life was achieved. The 95% CI for the mean values obtained were 93·0% to 93·6%.

The mean value for the oxygen saturation of haemoglobin observed in children aged less than 1 month (92·6%) was statistically different from that in children between 13 and 18 months of age (93·7%). Whether this small difference is clinically important remains to be clarified. The reason for the observed difference is not clear. Although we did not measure the proportion of fetal haemoglobin in any of the study subjects, the higher content expected in younger infants does not explain it, because the deviation to the left of the fetal haemoglobin saturation curve may produce higher oxygen saturation readings for fetal haemoglobin than for adult haemoglobin for a given $\mathrm{Pao_2}$,[6] and the difference observed by us was the opposite. Most authors agree that pulse oximetry provides reliable results even in presence of high concentrations of fetal haemoglobin.[1,3,15,16]

The studies conducted by Mok *et al* demonstrated that the normal oxygen saturation of haemoglobin can be lower during feeding and active sleep when compared with the results obtained in the same children during rest or quiet sleep.[12,13] For this reason we tried to obtain the saturation values with the children at rest. This was possible for the great majority of our subjects (79·4%). Even though it was not the main goal of the study, our data also suggest that the readings obtained during sleep are lower than during other physiological states. However, these results must be interpreted with caution, because the number of individuals sleeping during the measurement was small (eight), and the very low saturation observed in one of them (84%) would affect the mean value for this group. When the analysis was repeated without this very low reading, the mean oxygen saturation of haemoglobin in the group of children sleeping was lower than that observed in the other physiological states (92·1%), but was no longer significant. The practical effects of the various values found among children sleeping and awake (91·2% and between 93·3% and 93·5%, respectively) are probably small.

The validity of readings of the oxygen saturation of haemoglobin obtained in the 15 crying children deserves further discussion because of the possibility of error due to movement artifacts.[17] Several measurements were repeated because of signals indicating movement before obtaining the saturation figures. Obtaining saturation values with the N10 oximeter means that there is no interference with the measurement (even if the subject is crying). We included those values in order to make the results applicable to children who cry during the measurement. Although only 7·9% of our subjects were crying, the proportion of 'unsuccessful measurements' due to crying, restlessness, fear of the probe, lack of cooperation, and movement reported by other authors may be as high as 13% and 9% for infants aged less than 10 months between 1 and 6 years, respectively.[18]

CONCLUSIONS

We believe that the population of our study was representative of the population of healthy children of the city of Bogota and of other Latin American cities located at similar altitudes. We hope that the results of our study can be used with additional reference values for the interpretation of the readings for oxygen saturation of haemoglobin at high altitude.

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Narcolepsy

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Abstract

The symptom of excessive sleepiness in children and adolescents does not necessarily cause great concern to families and professionals involved in their care. Children may deny the symptom and minimise the adverse effects. These factors contribute to an underdiagnosis of narcolepsy in this age group when clinical diagnosis is difficult as associated symptoms may not have appeared or are hard to elicit. In this paper three children whose difficult behaviour contributed to the presentation of their sleep disorder are described.

The narcolepsy syndrome comprises sleep disturbance, cataplexy, sleep paralysis, and hypnagogic hallucinations, although all four symptoms occur only in a minority.[1 2] The sleep disturbance involves excessive daytime drowsiness with intermittent, irresistible naps and a disrupted pattern of nocturnal sleep. Estimates of the prevalence of the condition suggest that between two and nine per 10 000 of the general population are affected.[3] There is a strong link with HLA-DR2.[4] The condition is rarely diagnosed in childhood or early puberty, although single cases have been reported.[5 6] In a large series of patients only 4% of 400 adults had been diagnosed before the age of 15 years,[7] yet Navelet *et al* reported that the families of more than half of adult patients recalled that symptoms had begun by that age.[8]

The apparent under identification of narcolepsy in children and young adolescents is given added significance by the increasing evidence that patients with narcolepsy suffer significant psychosocial adversity and the possibility that early intervention may reduce this.[9 10] Kales *et al* detail the retrospectively self reported psychosocial adverse consequences of excessive sleepiness in childhood or adolsecence.[11] Many patients had school problems and reported that their teachers misinterpreted symptoms as laziness, indifference, or malingering. The authors suggest that these consequences, together with a lack of emotional expressivity cultivated by patients to prevent cataplexy, contribute to the high rate (50%) of minor psychopathology found in this and other studies of adult populations.[12 13]

In this paper we describe three consecutive cases of narcolepsy in childhood presenting to the Park Hospital for Children, Oxford, a specialist centre for childhood epilepsy, sleep disorders, and behavioural disturbance. They illustrate some of the diagnostic issues and management problems that may be encountered.

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Case reports

CASE 1

A boy aged 8 years was referred with a history of daytime sleepiness, irritability, and difficult behaviour. He had become increasingly sensitive, surly, and irritable after the birth of a sister one year earlier. When three months later the family moved home the boy resented the upheaval and found difficulty in settling and making new friends. His parents first noticed problems with daytime sleeping at around this time. Irresistible episodes of sleep, lasting from one to two hours, gradually increased in frequency to three or four times a day. He was often irritable on waking and his behaviour sometimes confused and disorientated. Sometimes he fell asleep while eating or even standing. His nocturnal sleep became restless, he was troubled by vivid dreams, and by a recurrence of nocturnal enuresis. He did not snore. At school he slept in quiet activities in class every day. Noting that during computing and games periods he was able to stay awake, his teachers had made the assumption that he was opting out of activities he disliked. They described him as academically bright and continuing to make good progress in class.

On interview he persistently denied that he slept during the day or had any problem with drowsiness. He gave no history of hypnogogic hallucination, cataplexy, or sleep paralysis. On admission to hospital for investigation the pattern of sleep disturbance and the denial of sleepiness continued. He would often remain standing for long periods during activities in order to prevent sleep. Although generally pleasant and cooperative, he became noticeably aggressive on waking from a daytime nap. Physical and neurological examination was normal. Investigations including thyroid function tests, 24 hour cassette recordings for electroencephalography (EEG), computed tomography, and magnetic resonance imaging (MRI) brain scans were normal. He was found to be of HLA type DR2.

Sleep recordings

All night polygraphic recordings of sleep over two consecutive nights were undertaken.[14] The physiological parameters measured included EEG, eye movements, and electromyelography for sleep staging as well as electrocardiography and periodic leg movements.[15] Simultaneous video recordings of nocturnal sleep and all night oximetry were also carried out. The results of the oximetry supported by video recording enabled obstructive sleep apnoea to be excluded.

The sleep recordings were analysed automatically using the Oxford Medilog sleep stager[16] and rechecked visually. The sleep architecture over both nights was stable with no significant differences in sleep stages. He went into rapid eye movement (REM) sleep within five minutes of sleep onset on both nights of the recording. His sleep was fragmented with frequent brief arousals and awakenings and he spent 16% of sleep time in the awake state or stage one sleep. This increase was at the expense of stage two sleep. Periodic leg movements, although increased, were not responsible for all arousals.

After the second night of recording a multiple sleep latency test was carried out, using standard protocol suggested by Carskadon *et al.*[17] Sleep onset occurred in less than five minutes in all five opportunities given and REM sleep within 10 minutes of sleep onset on four occasions. Taken together these sleep study findings were considered diagnostic of narcolepsy.

Management

After the sleep studies a detailed and age appropriate explanation of the diagnosis of narcolepsy was given to the boy and his parents over several meetings. The father was able to help his son overcome his initial denial and work positively on a management programme once he was discharged from hospital. This was facilitated by supportive family sessions and visits to the boy's school by hospital staff. As he was refreshed and able to concentrate well after a nap, a routine of three to four naps of 15 to 20 minutes' duration at fixed points in the day was established and was designed to help him to be alert in academic periods while minimising interference with social activities. In addition he was encouraged to follow a strict night time sleep routine to consolidate nocturnal sleep and advised not to get out of bed even if waking frequently.

As some daytime sleepiness persisted after these interventions, stimulant medication was prescribed in the form of mazindol 1 mg taken in the morning with food.[18] This produced improvement and 12 months after the diagnosis he continues to do well in school and remains alert during the day. His family report a reduction in irritability on waking and in his angry expression of sibling rivalry. He has not yet reported cataplexy or other associated symptoms.

CASE 2

A boy aged 12 years was referred by his paediatrician for investigation of behavioural disturbance and possible epilepsy. Four years earlier there had been a change in his disposition such that from being a relaxed and happy child he had become withdrawn, surly and truculent, had frequent temper outbursts, and was physically aggressive. On one occasion he struck a passer by who tried to prevent his breaking a shop window with a hammer. Both parents were profoundly deaf and this change in demeanour coincided with an appreciable deterioration in his father's hearing.

Episodes of daytime sleepiness started at 10 years of age. Initially they occurred at home when he was bored but gradually he started to fall asleep in unusual circumstances. He fell asleep during mealtimes and was once found asleep on the pavement outside a neighbour's house. If undisturbed he would sleep for three to four hours and would be irritable, aggressive, and moody if woken. There had been a number of episodes of confusion on waking. He did not snore and there was no definite history of cataplexy or sleep paralysis but he did report frequent nightmares. His appetite and weight had recently increased. At school his sleepiness was thought to be due to disinterest and laziness. His academic attainments had fallen dramatically and he had become withdrawn and socially isolated. Such was the extent of the difficulties in school that it was thought that his educational needs were best met away from mainstream school and transfer to residential special school had been arranged.

At interview he was argumentative and irritable with an abrupt and sullen manner. Although intermittently dozing off, he denied feeling sleepy and became angry when this denial was challenged. His general physical and neurological examination was normal. On admission for investigation his pattern of sleep disturbance and angry, oppositional behaviour in relation to daytime sleepiness was confirmed. Thyroid function tests, 24 hour cassette EEG, computed tomography, and MRI scans were normal. Nocturnal oximetry was normal. There was an increase in periodic leg movements. He was positive for HLA type DR2. Polysomnography showed disrupted sleep architecture consistent over two consecutive nights, with frequent arousals. The boy spent 27% of sleep time in wake or stage one sleep and entered REM sleep within five minutes of sleep onset. In the multiple sleep latency test sleep onset occurred in less than five minutes in all five opportunities given and sleep onset REM sleep occurred on two occasions. These findings were considered compatible with the diagnosis of narcolepsy.

Management

The diagnosis was discussed in detail with the boy and his family. He remained unable to accept the diagnosis or that daytime sleepiness posed any problem for him. He remained uncooperative with any intervention in hospital. With parental permission we discussed the implications with staff from the special residential school that he attended on discharge from hospital who were understanding and keen to help. The structured environment of a residential school allowed for the effective implementation of a strict nocturnal sleep routine and fixed naps to fit into the school day from the onset. At first he continued to deny problems and fought the desire to sleep by excessively argumentative and aggressive behaviour. However with continued support from school staff and the medical team he gradually, over a period of several months, became more amenable.

This allowed other treatment strategies to be employed. As he was overweight, he cooperated in the introduction of a weight reduction programme. He started a low energy diet that also incorporated the avoidance of pure sugars, which are known precipitants of sleep in narcolepsy,[19] and took up weight lifting with great zeal and success. This considerably reduced daytime sleepiness, which was further helped by a small dose of stimulant drug in the form of mazindol 1 mg in the morning after food. This combined programme resulted in a considerable improvement in his behaviour and level of daytime alertness and he continues to function well 18 months after diagnosis.

CASE 3

A boy aged 9 years was referred by his paediatrician for investigation of disturbed nocturnal sleep, excessive daytime sleepiness, and excessive appetite, all gradually increasing over two years. At the time of referral he was suddenly falling asleep for periods of 15 minutes to one hour, three to four times a day. If undisturbed he awoke refreshed but if aroused was often irritable and aggressive. His noctural sleep was restless with frequent jerkings and awakenings. There was no history of sleep paralysis, hypnagogic hallucinations, or cataplexy. There was considerable concern about his voracious appetite with bingeing, which had resulted in excessive weight gain in the previous year.

Epilepsy had been considered in the differential diagnosis because of an unexplained injurious fall from a bicycle a year previously and non-specific EEG changes in the awake record including excessive slow waves for age. There were also considerable pre-existing psychosocial problems. The boy's parents separated 18 months after his birth because of marital violence. His teenage mother had returned to live with her father and stepmother. The boy's behaviour had become the focus of considerable friction between the adult members of the family. At school he was disruptive in class with poor concentration and was chaotic and aggressive in the playground. He was intelligent but significantly under achieving. He often fell asleep in class and his teacher initially attempted to rouse him without success. He had been referred to a child guidance clinic where a diagnosis of conduct disturbance was made and sleep disturbance was ascribed to psychosocial problems. With the advice of the clinic the boy's behaviour had significantly improved in the months before his assessment for sleep problems.

On admission to hospital daytime episodes of sleepiness and restless nocturnal sleep were confirmed. No behaviour problems were encountered during his stay and he interacted well with peers and staff. His general and neurological examination was normal. He was of HLA type DR2. Investigations, including 24 hour cassette EEG recordings, computed tomography, and oximetry were normal. Polysomnography and the multiple sleep latency test produced a pattern strongly suggestive of narcolepsy with fragmented noctural sleep architecture, a relative reduction in stage two sleep, and rapid entry into REM sleep at night. In four opportunities offered to sleep during the multiple sleep latency test there was an increase in periodic leg jerks but not sufficient to explain the extent of nocturnal arousal.

Management

Repeated explanation of these findings were given to the boy and his family, who found it initially very difficult to accept the diagnosis of narcolepsy. For three years the boy denied problems with daytime sleepiness and his family gave no commitment to a sleep management programme. However, at secondary school teachers construed his periods of sleepiness as 'opting out' and he was placed in a class for children with learning difficulties. The issue of his school progress was raised in a case conference. As a result the boy began to accept the need for active management of his daytime sleepiness. His teachers felt that fixed naps during the day would be impractical in a comprehensive school setting. His programme therefore included a weight reducing diet with avoidance of pure sugars, good nocturnal sleep hygiene, and stimulant medication (mazindol 2 mg) in the morning after food. He took responsibility for compliance and monitoring his own progress. At follow up there has been significant improvement in his level of alertness during the day and his progress in school is encouraging. Two episodes of possible cateplexy occurred about one year after diagnosis when his legs felt unsteady during an outburst of laughter.

Discussion

These cases illustrate many of the considerable difficulties in the diagnosis of narcolepsy in children and young adolescents. Recognition of the problem may be delayed for a number of reasons because children, like adults, find the occurrence of daytime sleepiness embarassing as it is often associated with indolence, incompetence, or social irresponsibility. To avoid teasing or admonition children deny symptoms and develop a variety of strategies to stave off sleep. Some of these strategies may be maladaptive, for example argumentative or disruptive class behaviour. Parental knowledge about normal sleep development is often sparse and in the absence of cataplexy, school failure, or appreciable behavioural difficulty anxiety about daytime sleepiness may be insufficient to bring the matter to medical attention.[8] The same environmental factors influence daytime sleepiness in narcoleptic patients and normal people. As patients tend to fall asleep in quiet lessons and after lunch rather than during periods of physical activity, teachers tend to initially attribute symptoms to disinterest, laziness, or social problems at home. This attribution may inhibit recognition of the problem until symptoms become considerable. Finally, as the condition is relatively rare before puberty few paediatricians or child psychiatrists have much experience of its presentation.

Guilleminault has described the differential diagnosis of daytime sleepiness in children,[20] and Stores has pointed to confusions concerning sleep disorders and the epilepsies.[21] Though in adult or adolescent patients a clinical diagnosis of narcoleptic syndrome can often be made on the basis of detailed history taking alone, this is rarely the case with children, and in none of this series was it possible. All gave a history of a change in the quality of nocturnal sleep but a history of brief refreshing episodes of daytime sleep characteristic of narcolepsy was not obtained.[1] Rather, the daytime naps were long and unrefreshing perhaps because sleep had been resisted for long periods. On awakening the boys were often irritable and disorientated. It proved difficult also to elicit subjective experiences involved in sleep paralysis, hypnogogic hallucination, or cataplexy.

The short latency before REM sleep with fragmentation of sleep structure by frequent nocturnal arousals seen in the three children is characteristic of narcolepsy. Other causes of a short REM latency are sleep deprivation and depressive illness in adults. An increase in periodic leg movements or nocturnal myoclonus is reported in narcolepsy and was seen in all three children. The frequency of these movements was not sufficient to account for the frequency of nocturnal arousal found. The multiple sleep latency test is an objective measure of daytime sleepiness standardised by Carskadon *et al.*[17] A mean sleep latency of less than five minutes suggests pathological excessive daytime sleepiness and occurs in narcolepsy and occasionally in central nervous system hypersomnia and severe obstructive sleep apnoea. Two or more episodes of REM sleep occurring within 10 minutes of sleep onset (SOREM) on the five opportunities given to sleep during the day is considered diagnostic of narcolepsy. The mean sleep latency in all three children was less than five minutes and all had more than two episodes of SOREM.

The children's denial of symptoms, diagnosis, and problems became the greatest single barrier to effective management. Families found it difficult to accept a diagnosis with life long implications based solely on a sleep disturbance. We found it important to continue to support the family and child with regular follow up sessions. The cooperation of the children's school proved crucial in management. Teachers welcomed contact and explanation of the nature of the problem and when schools took up the suggestion of a nap programme there was undoubted success.[22] All three children required a small amount of stimulant medication to allow effective daytime function. Stimulants were not started until other management strategies had been fully explored. A very small once daily dose (1 or 2 mg) of mazindol given in the mornings after breakfast, on school days only, was found to be sufficient. No adverse effects have been encountered and the drug regimen has been well tolerated but requires continued monitoring.[23]

The behaviour problems exhibited by these boys were at times severe. There were pre-existing psychosocial and familial variables that undoubtedly contributed to them. Problems with conduct, control, and peer interactions were reported by families and schools before the onset of other symptoms in all three cases and may simply have been coincidental factors leading to early referral. However the onset of narcoleptic symptoms was temporally associated with a significant exacerbation of behavioural difficult. A number of mechanisms could be postulated for this. Firstly, there may be an increase in irritability, disinhibition, and disorientation associated with constant excessive drowsiness and periods of 'microsleep'.[24] Secondly, Roth has reviewed the association between narcolepsy and depression.[25] Mood changes might arise from neurobiological mechanisms associated with the as yet unknown aetiology of narcolepsy, or as a reaction to the disabling cognitive, emotional, and social effects of chronic sleepiness.[9 10 26] Although none of the boys met diagnostic criteria for depressive disorder, all tended to be low in mood, irritable, and socially withdrawn. Lastly it is possible that anxiety among the boy's carers after the onset of unusual symptoms led to more inconsistent management of behavioural problems at home, at school, and in hospital.

As narcolepsy is a life long condition early diagnosis would be of value if it could be demonstrated that psychosocial and educational problems could be reduced as a result. This might be achieved both through symptom control and educational approaches. These three cases illustrate some of the difficulties that may lie ahead in any attempt to achieve such a reduction. Research into management and educational strategies specifically for young people is needed. Studies are needed relating outcome in terms of employment and psychosocial factors to age and delay in diagnosis and to medical and educational intervention. With this information a better understanding of the aetiology and management of associated behavioural and mood problems may be achieved. As the number of children with the condition is small it may be necessary for specialist centres with appropriate resources for diagnosis and management to evolve. Difficulties for these patients may best be minimised by greater public awareness of the condition and knowledge of normal sleep development in children.

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Postnatal encephaloclastic porencephaly—a new lesion?

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Abstract

A previously unrecognised and distinctive pattern of severe brain injury in extreme preterm neonates was observed recently. Fifteen neonates of birth weight 600–1270 g and gestation of 24–32 weeks showed relatively late development on cerebral ultrasound scan of extensive dense and cystic lesions involving the periphery of the brain. The extent of the changes was confirmed at postmortem examination in 11 babies. These changes have been called encephaloclastic porencephaly. The population of babies in whom this has occurred and their clinical outcome has been reviewed, with comparison between the evolution of the ultrasound changes and pathological findings at postmortem examination.

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The susceptibility of the brain in the sick premature infant to insult is well recognised, with important consequent morbidity and mortality. Improved techniques in brain ultrasonography have led to early recognition of brain injury, and in particular certain patterns of injury have been well defined in the literature over recent years.[1, 2] In the patient who suffers cerebral ischaemia periventricular leucomalacia is characteristic, but in the mature infant subcortical leucomalacia is more typical. Current evidence suggests that the site of the lesion is determined by the development and maturation of the cerebral arterial blood supply.[3–5]

Recently we have observed a new pattern of injury in a series of 15 preterm neonates at Birmingham Maternity Hospital. In these infants we observed the relatively late development of extensive echodense and cystic lesions involving the periphery of the cerebrum. The pattern seen on ultrasonography and confirmed at postmortem examination in two thirds of cases has not previously been reported in liveborn infants, although pathologically it has similarities with the lesion of hydranencephaly in the fetus.[6] The population of neonates is reviewed and the evolution of ultrasound changes and correlation with pathological findings described.

Subjects and methods

The neonatal intensive care unit at Birmingham Maternity Hospital is the regional referral unit for the West Midlands. All neonates admitted to intensive care undergo cerebral ultrasound scanning twice a week and later once a week when the infant is clinically stable. The majority of scans were performed by one experienced observer (PRP). A Hewlett Packard ultrasound imaging system with a 5 mHz phased focused array transducer was used. The anterior fontanelle was used as an acoustic window. The method used and our experience at this unit has been reported previously.[1]

During the study period September 1988 to April 1990, 265 babies of birth weight <1500 g were admitted to our unit. In 15 neonates a new pattern of brain injury was noted. Clinical data were drawn for these 15 neonates from contemporary case notes and the evolution of ultrasound scan appearances analysed.

A postmortem examination was performed by the regional perinatal pathologist (DIR) in 11 of the 14 babies that have died.

Results

(1) CLINICAL DETAILS AND OUTCOME

Clinical details of the neonates under discussion are outlined in table 1. All were sick preterm

Table 1 Clinical details of the neonates

Infant No	*Gestation (weeks)*	*Birth weight (g)*	*No of days ventilated*	*No with mean blood pressure <30 mm Hg in first 24 hours*	*Age at death (days)*
1	25	600	27	Yes	27
2	28	1060	9	No	42
3	26	1230	14	Yes	19
4	27	810	14	Yes	31
5	24	630	13	Yes	13
6	26	790	9	No	21
7	26	990	7	No	34
8	27	920	25	Yes	25
9	26	1240	21	Yes	39
10	32	1270	12	No	23
11	26	700	13	No	22
12	29	1260	3	No	Alive
13	27	1110	6	Yes	39
14	28	690	14	No	39
15	28	850	32	No	31

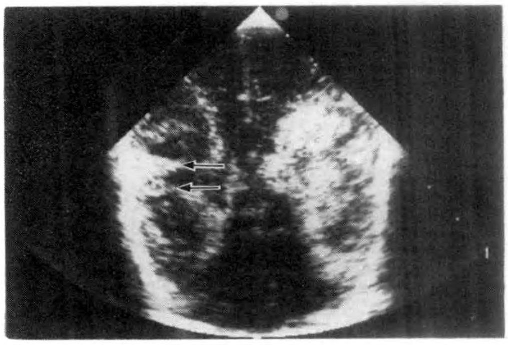

Figure 1 Posterior coronal section showing deep echodense sulci on the left (arrowed).

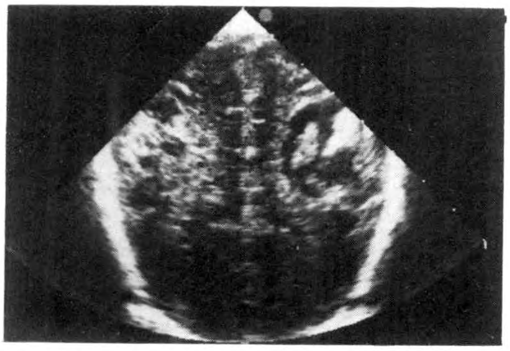

Figure 2 Posterior coronal section showing widespread cystic change in both cerebral hemispheres.

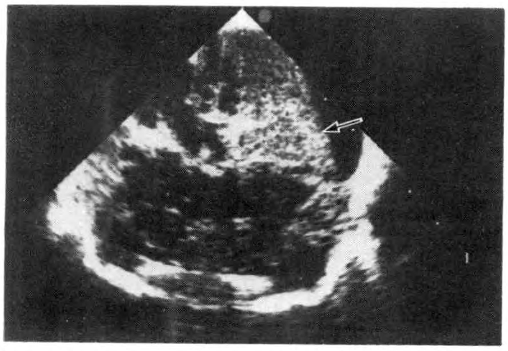

Figure 3 Coronal ultrasound showing shrinkage of brain away from skull (arrowed).

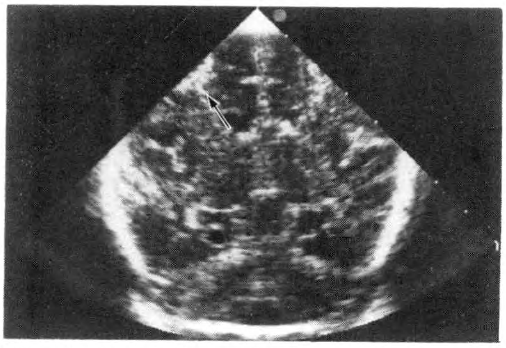

Figure 4 Coronal ultrasound scan showing peripheral wedge shaped echodensity on the left (arrowed).

neonates whose clinical histories bore all the markers of neonatal intensive care. They were of mean gestation 27 weeks (range 24–32 weeks) and mean birth weight 940 g (range 600–1270 g). Fourteen required ventilation from birth for a mean duration of 15 days. Seven required colloid for the treatment of mean blood pressure <30 mm Hg in the first 24 hours of life but none required inotropic agents. All underwent arterial cannulation. Eleven had a patent ductus arteriosus, seven received indomethacin, and one required surgery.

Outcome was extremely poor with 14 of the 15 neonates dying. All were profoundly abnormal neurologically before they died and eight required treatment for frank convulsions. The one survivor has severe neurological deficit at 12 months.

(2) ULTRASOUND SCAN APPEARANCES

The cerebral ultrasound appearances were characterised by irregular echodense areas extending from the ventricles to the skull margin. They were bilateral, typically affecting the parietal lobes and sparing the medial parts of the hemisphere bordering the longitudinal fissure. Peripherally there were finger like projections, which represent deep echodense sulci, and these together with the medial sparing give a striking characteristic appearance on posterior coronal sections (fig 1).

This appearance was followed by gross cystic changes (fig 2) and sometimes shrinkage of the brain (fig 3). In three cases where evolution of these lesions was observed most closely the earliest changes were cortical wedge shaped densities (fig 4) that progressed rapidly to the

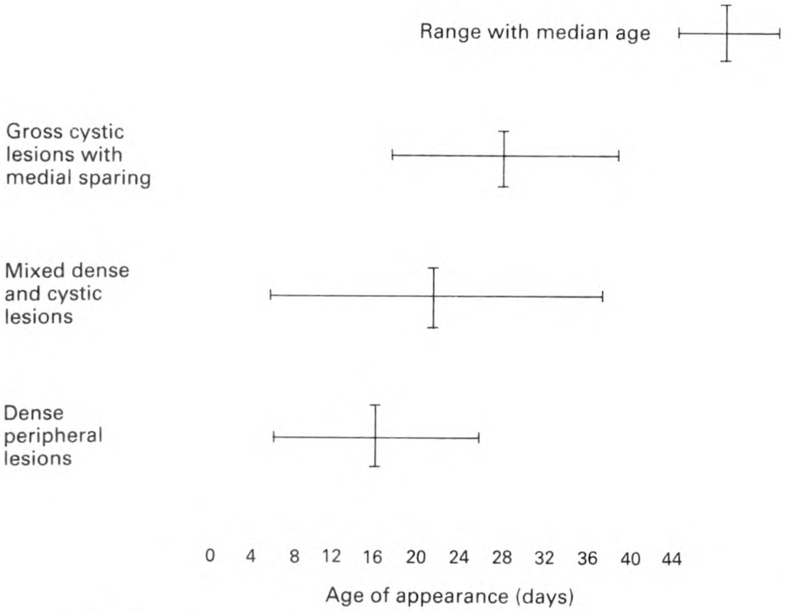

Figure 5 Evolution of ultrasound changes.

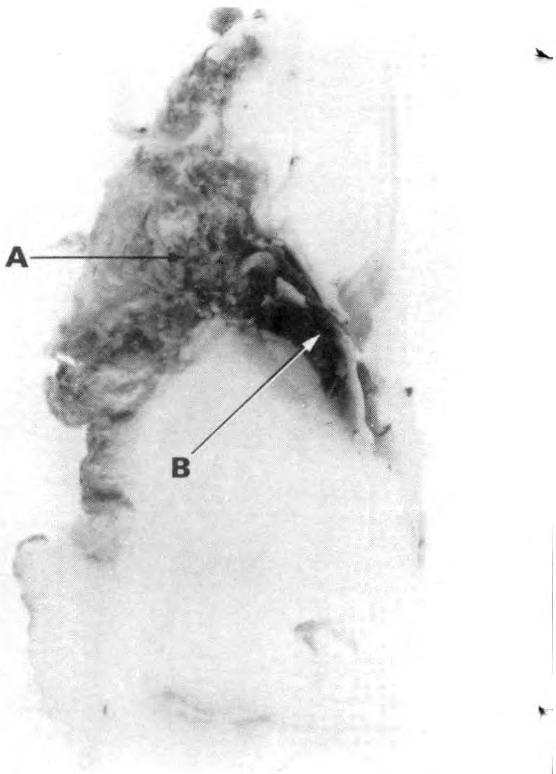

Figure 6 Case 5: coronal section left cerebral hemisphere. Necrotic wedge shaped lesion (A) extending from the cortex to the apex of the lateral ventricle. There is a subependymal haemorrhage in the inferolateral wall of the ventricle (B).

typical mixed cystic and dense lesions. The time of appearance of these changes is shown in fig 5. Other ultrasound abnormalities were present in five babies, namely subependymal haemorrhages alone in three (numbers 4, 9, and 15), a subependymal haemorrhage and periventricular leucomalacia in one (number 7), and a subependymal haemorrhage, intraventricular haemorrhage, and periventricular leucomalacia in another (number 11). In all these five babies these scan appearances were well established and stable at the time when new lesions appeared.

(3) PATHOLOGY (SEE TABLE 2)

The characteristic lesion in the majority of these babies was full thickness necrosis of the cerebral cortex and underlying white matter resulting in communication of the ventricular system with the subarachnoid space (fig 6), which we have termed encephaloclastic porencephaly after the convention of Yakovlev and Wadsworth.[7] Typically the area around the sulcus centralis, sulcus lateralis and insula were involved, although in the more extensive lesions the frontal, parietal, and occipital lobes were affected with relative sparing of the medial surfaces (fig 7). The extent of the lesions varied from relatively narrow clefts to very extensive loss of the superolateral portions of the cerebral hemispheres. In the majority of cases subarachnoid and/or cortical haemorrhages overlay the necrotic lesions (fig 8). Mature lesions typically showed rounded edges to the cortical defects (fig 9) with ragged linings to the deeper surfaces. Microscopy revealed a phagocytic and glial reaction that in many instances was more extensive and

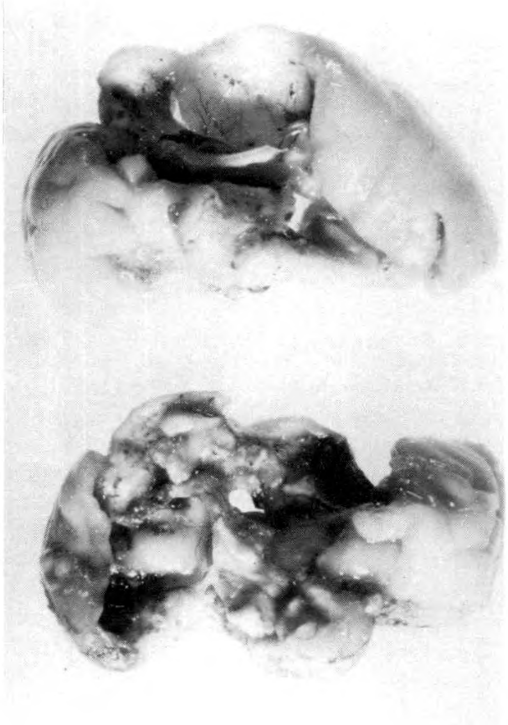

Figure 7 Case 4: cerebral hemispheres viewed from the lateral surfaces. End stage lesions with massive destruction of the cortex and cerebral white matter with preservation of the medial surfaces can be seen.

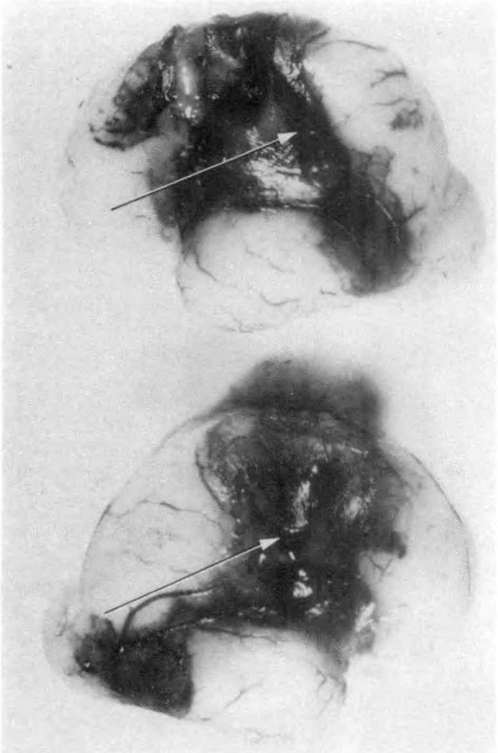

Figure 8 Case 5: lateral surfaces of the cerebral hemispheres. Subarachnoid haemorrhages overlying necrotic lesions have led to collapse of the hemispheres (arrowed).

Table 2 Pathological lesions in cerebral hemispheres by extent and site. Lesions were present in both hemispheres in all cases but differed in degree

Infant No	*Subarachnoid or cortical haemorrhage*	*Cortical necrosis*			*Site*			*Other lesions*
		Superficial	*White matter*	*Full thickness*	*Frontal*	*Temporoparietal*	*Occipital*	
1	No postmortem examination							
2	−	−	−	+	+	+	+	
3	+	−	−	+	−	+	+	
4	−	−	−	+	+	+	+	
5	+	+	+	+	−	+	−	
6	+	+	+	+	−	+	+	Old PVL
7	+	−	−	+	−	+	−	Cystic PVL
8	No postmortem examination							
9	Brain disintegrated at postmortem examination							
10	No postmortem examination							
11	+	−	−	+	−	+	+	
12	Alive							
13	+	−	−	+	+	+	+	
14	+	−	+	+	−	+	−	
15	+	−	+	+	+	+	−	

PVL=periventricular leucomalacia.

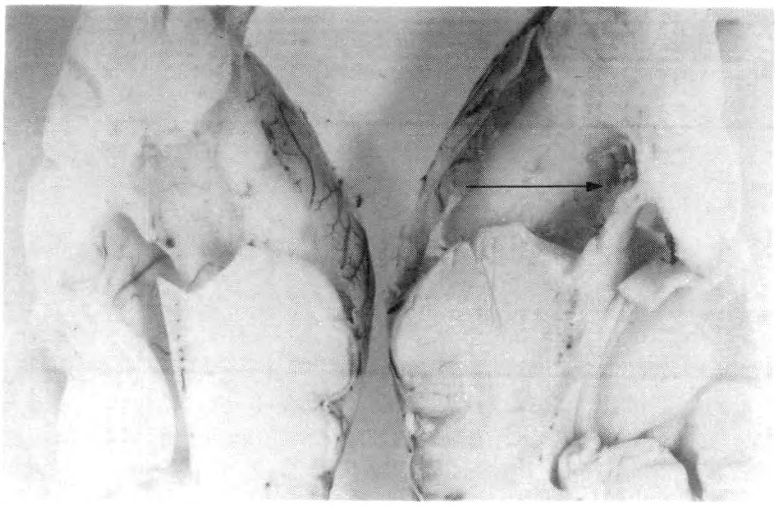

Figure 9 Case 14: coronal section of the cerebral hemispheres. Older lesions with rounded cortical margins can be seen. The partial thickness lesion has a ragged deep lining (arrowed).

advanced at the peripheral part of the lesion consistent with a centripetal evolution. The earlier lesions were associated with small subarachnoid haemorrhages and perivascular haemorrhages in the underlying cortex with a radial distribution. The pathology will be described in more detail elsewhere.

(4) CORRELATION BETWEEN ULTRASOUND CHANGES AND PATHOLOGY

In all cases where postmortem examination of the brain was performed there was good correlation with the last antemortem ultrasound scan. Extensive white matter involvement seen on ultrasound scan was confirmed with full thickness necrosis and involvement of both cerebral hemispheres seen in all cases. The initial peripheral involvement suggested on ultrasound was also supported at postmortem examination in cases where changes were more advanced to the periphery of lesions.

Discussion

During the 20 month period from September 1988–August 1990 at the Birmingham Maternity Hospital there were 15 neonates who showed a different pattern of severe brain injury to that previously described. Characteristically, these changes appeared late in the neonatal course. They were extensive, bilateral, and involved the periphery of the brain. Pathological findings confirmed ultrasound appearances, with full thickness necrosis of cerebral cortex and white matter. These findings are not in keeping with the classic pattern of brain injury previously described.

Periventricular leucomalacia is well recognised in the preterm infant and occurs in the watershed zones of arterial supply in the deep white matter of the brain.[3–6 8 9] Possible variations in white matter injury in these infants has been reported recently[10] but none in the pattern that we have described here. The characteristics of encephaloclastic porencephaly as we have seen are (i) an initial peripheral lesion, (ii) centripetal extension, and (iii) destruction of the cerebral mantle with relative sparing of the medial structures seen at postmortem, resembling hydranencephaly.[6] Encephaloclastic porencephaly has been previously described as the response of the brain to insult in the second trimester at a time when neuronal migration is complete but before glial reactivity is well developed.[11] Such lesions have been described in term infants who present at birth or soon after when clinical neurological symptoms have been recognised.[12]

Despite the wealth of literature on neonatal cranial ultrasound,[1 2 13–16] postnatal encephaloclastic porencephaly has not been previously described. The exact aetiology remains obscure. The neonatal course of the infants described here is typical of any neonate of birth weight <1500 g requiring intensive care, and there is no new procedure or technique that has been used. The presence of extensive necrosis is strongly suggestive of ischaemic injury, although the peripheral lesions are hard to explain in the context of our current understanding of ischaemic injury in the preterm brain. It is possible that with improved techniques and understanding of neonatal intensive care and the subsequent protracted survival of these neonates, early pathological changes not previously detectable on ultrasound scan are now becoming apparent at a later date. In this series of babies no insult to the brain has been identified and it is not possible to time the exact onset of the lesions. It seems probable that they represent the effects of an as yet unidentified postnatal event.

Postnatal encephaloclastic porencephaly carries an extremely poor prognosis. All but one of our infants died and before death eight had evidence of neurological abnormality requiring treatment for frank seizures. The only survivor had severe neurological deficit at follow up at 12 months.

In conclusion we report a new distinctive pattern of preterm brain injury, encephaloclastic porencephaly. Regular cerebral ultrasound scanning enables early recognition, with good correlation with pathological data.

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Meningococcal disease and the flu

The meningococcus is usually a peaceable organism sitting quietly in the nasopharynx and seemingly bearing no grudge. Why then does it become so malign all of a sudden? Variations in virulence may provide some explanation and clearly there are host and environmental factors involved in the propensity for young children. It has been suggested for a long time that upper respiratory virus infections might predispose to meningococcal disease by either facilitating the entry of the bacterium into the tissues and then into the blood or immune suppression.

In the last month of 1989 and the first of 1990 there was an epidemic of influenza A in England and Wales followed by an increase in meningococcal disease as judged by the number of isolates submitted to the Meningococcal Reference Laboratory. Data presented in the *Lancet* (Keith AV Cartwright and colleagues, 1991;**338**:554–7) showed that the interval between the two epidemics was about two weeks. Similarly timed increases in meningococcal disease also followed influenza epidemics in 1976 and 1957. The *Lancet* paper presents other less convincing data in addition to the epidemiological findings. A serum antibody titre to influenza A/England of 80 or more was found in 18·5% of 54 normal schoolchildren before the influenza epidemic, in 9% of control sera taken during or after the epidemic, in 28% of 43 patients convalescing from meningococcal disease, and in 91% of 23 people convalescing from influenza. The authors conclude that these serological data support an association between meningococcal disease and recent influenza (odds ratio about 4) but the twofold difference in positive rates in the two populations of control sera to my mind casts doubt on the validity of the conclusion. If 18% can by chance become 9% it can presumably by the same chance become 28%. A simultaneous questionnaire study of the incidence of influenzal symptoms before the meningococcal outbreak in cases and controls gave equivocal results and had little scientific validity.

It seems, therefore, that there is epidemiological evidence from three different years that an influenza epidemic may be followed two weeks later by an increase in meningococcal disease. The risk is very small, however; the authors estimate that 100 000 cases of influenza might give rise to one case of meningococcal disease. On that basis it would be necessary to immunise a million people against influenza to prevent a single case of postinfluenzal meningococcal disease (assuming that the influenza would affected one in 10 of the population) and no changes to current immunisation policy are recommended as a result of this work.

The subjects of the serological study were all over 10 years old and the significance of influenza for meningococcal disease in young children is uncertain. Meningococci sent to the Meningococcal Reference Laboratory after the influenza epidemic were less commonly from children under the age of 10 than usual, suggesting that any predisposing effect of influenza may be less common in younger children. The work is of theoretical interest but it seems to offer no obvious insights as regards the prevention of meningococcal disease in children.

ARCHIVIST

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Effect of positioning on the breathing pattern of preterm infants

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Abstract

Respiration, as judged by gas exchange and pulmonary function, is improved in preterm infants kept in the prone rather than the supine position. The influence of position on the breathing pattern as documented by the pneumogram was studied in 14 stable preterm infants with recent clinical apnoea. Ten of the infants had oximetry and nasal flow studies simultaneously with the impedance pneumogram. Each infant had consecutive nocturnal pneumograms, one in the prone, one in the supine position. The infants were kept for more than six hours in the assigned position.

A significant increase in apnoea density and in periodic breathing was found in the supine *v* the prone position (mean (SE) 4·5 (0·7)% *v* 2·5 (0·5)%, and 13·6 (3·2)% *v* 7·7 (2·2)%, respectively). There was no positional difference in the incidence of bradycardia and prolonged apnoea. The examination of obstructive apnoea, mixed apnoea, and cyanotic spells did not reveal a consistent disparity between the two positions.

These findings indicate an increase in central apnoea in preterm infants kept predominantly in the supine position. Possible relations of positional changes to lung mechanics are discussed. When evaluating pneumograms, attention must be given to the position in which they were performed.

Clinical experience suggests that preterm infants breathe better when kept prone. Several investigators have shown that gas exchange as evidenced by arterial tension of oxygen and carbon dioxide (Pao_2, and $Paco_2$), is better in the prone than in the supine position,[1–3] and pulmonary function tests improve when preterm infants are changed from lying supine to prone.[3 4] Kravitz *et al* found an increase in respiratory rate in the prone versus the supine position in preterm infants.[5] This study was undertaken to examine the influence of position on the breathing pattern, as documented by the pneumogram, in preterm infants who had recent apnoea and bradycardia, with the assumption that all types of apnoea would be increased in the supine position.

Methods

Fourteen preterm infants (gestational age mean (SD) 29·7 (2·8) weeks, range 26–36 weeks, and birth weight mean (SD) 1381 (474) g, range 840–2290 g) who had recent clinical apnoea but were otherwise healthy were enrolled in the study, after informed consent was obtained from the parents. Nine infants had previous respiratory distress syndrome requiring up to eight days of intubation. Infants with bronchopulmonary dysplasia were excluded from the study. The infants did not require respiratory support or oxygen, and were all enterally fed (bolus feedings either by nipple or by intermittent gavage) at the time of the study. Eight infants received maintenance methylxanthine therapy and had stable therapeutic blood concentrations.

The breathing pattern was studied by the cardiorespirogram (pneumogram). Each infant had consecutive nocturnal 12 hour impedance pneumograms: one while in the prone and one in the supine position. The order was assigned at random, by sealed envelopes. When assigned to the prone position, infants were kept in the assigned position all night, except during feeding. When assigned to the supine position, infants were kept supine except for one hour after feeding, when they were placed prone to facilitate burping and prevent aspiration. The infants spent the majority of the study period in the assigned position. No attempt was made to keep the head in midline position. In general, the head was turned to the side 75–90° when prone and about 45° when supine. The infant's neck and shoulders were supported to avoid neck flexion.

Pneumograms were analysed using a Pediatric Diagnostic Service computer program, as developed by Kelly *et al.*[6] Apnoea episodes were defined as cessation of breathing for ≥6 seconds. Apnoea density (AD_6) was defined as the percentage of apnoea time while the infant was quite ($AD_6 = 100 \times$ seconds of apnoea/seconds of quiet state). The infant was considered to be quiet when heart rate and respiratory pattern were stable, without artefacts. Bradycardia was defined as a decrease in heart rate below 100 beats/minute for ≥5 seconds. Periodic breathing was defined as three episodes of apnoea ≥3 seconds interrupted by respiration lasting ≤20 seconds.

Central apnoea was defined as a cessation of both breathing movements and nasal airflow. Obstructive apnoea was defined as a cessation of nasal flow while breathing movements continued with a fall in oxygen saturation lasting ≥5 seconds. Mixed apnoea spells were defined as obstructive breaths combined with irregular breathing movements. The latter were usually of longer duration along with a significant drop in oxygen saturation. Desaturation was defined as a drop in oxygen saturation to <87·5%, lasting ≥10 seconds.

Obstructive and mixed apnoea was examined in 10 of the 14 infants by recordings of nasal flow and oximetry, obtained simultaneously with the impedance pneumogram. Nasal air flow was measured by end tidal carbon dioxide (Engstrom Eliza carbon dioxide analyzer, Astro Med); oximetry was measured by a Nellcor pulse oximeter. These parameters, as well as heart rate, breathing movements, and heart rate off the oximeter, were recorded on a multichannel recorder. Obstructive or mixed apnoea periods of $\geq$6 seconds' duration and oxygen desaturation episodes were counted manually by one of the investigators (JL), who was blinded regarding the position during the recordings. Episodes of generalised body movements as evidenced by abrupt changes and irregularities in heart rate, or drops in heart rate on the oximeter not concurring with bradycardia, were excluded from the analysis.

Results were shown as mean (SE). To compare the prone with the supine position the Student's *t* test for paired samples was used and differences were considered significant when $p<0{\cdot}05$.

Results

Fourteen infants were studied at mean (SD) 34·4 (1·9) weeks (range 32–36 weeks) postconceptional age. The infants age at the time of study ranged between 1 and 8·5 weeks (weight range 1270–2250 g). More mature infants were studied at an earlier age.

Table 1 Impedance pneumogram analysis (n=14). Values are shown as mean (SE)

	Supine	*Prone*	*Mean difference supine–prone*	*p Value*
Apnoea episodes* $\geq$6 s	175·5 (28·5)	110·3 (22·2)	65·2 (20·9)	0·008
Apnoea episodes 11–15 s	4·6 (1·3)	2·4 (0·9)	2·2 (0·9)	0·032
Apnoea episodes $\geq$15 s	2·3 (1·0)	0·4 (0·2)	1·9 (1·0)	0·074
Apnoea in non-periodic breathing (s)	487 (56)	364 (47)	123 (58)	0·05
Apnoea in periodic breathing (s)	840 (190)	451 (140)	389 (145)	0·018
All apnoea (s)	1327 (210)	815 (162)	512 (163)	0·008
Bradycardia episodes	3·4 (1·0)	3·8 (1·5)	−0·4 (0·8)	0·65
AD_6 total	4·5 (0·7)	2·5 (0·5)	2·0 (0·6)	0·01
Periodic breathing (% of quiet)	13·6 (3·2)	7·7 (2·2)	5·9 (2·1)	0·015
Quiet time (min)	501 (20)	522 (23)	−21 (22)	0·40

*Episodes are shown as number/recording.
AD_6 (Apnoea density) is apnoea episodes $\geq$6 seconds expressed as the percentage of quiet time.

Table 2 Effect of feeding on the postprandial impedance pneumogram (n=14). Values are shown as mean (SE)

	Supine group	*Prone group*	*Mean difference supine–prone*	*p Value*
Apnoea in non-periodic breathing (s)	213 (39)	116 (17)	97 (35)	0·015
Apnoea in periodic breathing (s)	240 (70)	62 (21)	178 (63)	0·014
All apnoea (s)	453 (100)	186 (37)	267 (88)	0·01
Apnoea episodes $\geq$11 s	4·3 (1·7)	0·9 (0·4)	3·4 (1·4)	0·031

Table 3 Duration of spells of obstructive or mixed apnoea and of desaturation in seconds during a 12 hour period and during feeding and postprandial periods (n=10). Values are shown as mean (SE)

	Supine	*Prone*	*Mean difference supine–prone*	*p Value*
All mixed apnoea	137 (57)	95 (25)	42 (51)	0·50
All obstructive apnoea	703 (146)	615 (86)	88 (108)	0·45
All desaturation*	330 (95)	277 (65)	53 (79)	0·50
Feeding and postprandial period				
Mixed apnoea	66 (23)	43 (14)	23 (22)	0·45
Obstructive apnoea	225 (63)	258 (66)	33 (33)	0·30
Desaturation	180 (75)	167 (48)	13 (78)	0·87

*Desaturation is oxygen saturation of <87·5%, lasting $\geq$10 seconds.

Table 1 describes the differences in the impedance pneumogram. There was a significant increase of apnoea density in the supine versus the prone position ($p=0{\cdot}01$). Supine positioning resulted in a 77% increase in periodic breathing ($p=0{\cdot}015$). There was no positional difference in respiratory rate or in heart rate.

The mean (SD) number of feeds per infant was 4 (1·1) during the 12 hour recordings. Table 2 shows the effect of bolus feedings on the pneumogram, as seen one hour postprandially. There was a significant increase in postprandial apnoea during the night the infants were nursed supine compared with the night they were nursed prone. The increase in apnoea was as pronounced in non-periodic breathing as in periodic breathing ($p=0{\cdot}015$).

No large or consistent positional difference was demonstrated in the duration of spells of obstructive or mixed apnoea nor in the duration of oxygen desaturation episodes in the 10 infants examined (table 3).

Discussion

This study demonstrates an increase in the incidence of apnoea in the supine compared with the prone position. The positional difference existed both during periods of non-periodic breathing as well as during periods of periodic breathing. The increase in apnoea while in the supine position presented as an increase in central apnoea as demonstrated by the AD_6 total. The positional difference in the impedance pneumogram is not secondary to the order in which the pneumograms were obtained nor to interval improvement in apnoea because the order of the study positions was random. Moreover, another study did not find a significant difference between consecutive pneumograms in a large number of patients.[7]

The mechanism of the increase in central apnoea demonstrated in the supine position is not entirely clear. Respiration in the preterm infant is regulated by mechanoreceptors mediated via vagal fibres (the Hering-Breuer reflex), peripheral and central chemoreceptors, and a suprapontine respiratory centre.[8] Preterm infants, while in active sleep, exhibit asynchronous movements of the intercostal muscles in relation to diaphragmatic contraction. The resulting rib cage distortion may cause a decrease in functional residual capacity and in pulmonary oxygen reserve.[8] This would render the higher respiratory centre more prone to hypoxia, leading to respiratory depression and apnoea. Martin *et al* have found a very significant increase of asynchronous breathing coupled with decreased oxygenation in the supine compared with the prone position.[1] A compensatory increase of diaphragmatic movements during asynchronous breathing may also lead to increased diaphragmatic fatigue.[8 9] Prone positioning allows the posterior portion of the diaphragm, which has a lesser curvature and more effective respiratory movements, to function unopposed by abdominal pressure.[3 10] Diaphragmatic fatigue, which has been observed in relation to clinical apnoea,[11 12] may thus be more pronounced in the supine position.

The postprandial comparison of the two positions could be further evidence of the role of diaphragmatic fatigue. Feeding preterm infants has been shown to decrease lung volume,[13] and to increase diaphragmatic work.[14] When the infants were studied in the supine position they were prone for one hour postprandially. However, comparing the postprandial hour between the two positions reveals more apnoea in the infants who were supine before feeding. This suggests that the supine position compromises diaphragmatic function so that a further work load, as seen with feedings, is not well tolerated. This would then lead to an increase in apnoea.

The finding that the increase in apnoea in the supine position presented primarily as the central type was surprising. A study comparing the supine with the sitting position in infants demonstrated an increase in airway resistance when supine, especially when the neck was flexed.[15] The pneumogram study of Miller *et al* of babies in the supine position revealed that about half of the apnoea episodes were obstructive or mixed, and could be abolished by continuous positive airway pressure.[16] Our finding that apnoea spells of an obstructive nature were not consistently increased when supine may be due to our strict avoidance of neck flexion in this position. A contribution of increased gastro-oesophageal reflux to the apnoea spells while supine is also unlikely, as the increase in spells was largely of the central type.

A tendency for an increase in airway resistance below the neck in the supine position compared with the prone in intubated preterm infants was found by Wagaman *et al.*[3] We do not know whether this, too, might contribute to diaphragmatic fatigue presenting with central apnoea, as indeed nine of the smaller infants in the present study had previous respiratory distress syndrome, albeit without consequential chronic lung disease. In contrast to previous studies,[1–4] we did not find a positional difference in episodes of oxygen desaturation in the 10 infants studied. This does, however, concur with the lack of positional difference in prolonged apnoea and bradycardia spells in our patients.

In conclusion, we have demonstrated an increase in central apnoea in preterm infants with clinical apnoea cared for predominantly in the supine position compared with the prone position. As there was no positional difference in prolonged apnoea or bradycardia spells, the clinical implication of our results is uncertain, although the increase in periodic breathing in the supine position deserves attention. The main significance of this study resides in the finding of disadvantage of the supine versus the prone position, which is in agreement with the observations during gas exchange and pulmonary function tests.[1–4] We speculate that decreased lung volume and increased diaphragmatic work when supine are important in the genesis of the positional difference in apnoea density. There is a need for further studies correlating positional pneumograms with pulmonary function and diaphragmatic mechanics. Finally, when evaluating pneumograms, the position of the infant during the major part of the study must be known.

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An indirect calorimetry system for ventilator dependent very low birthweight infants

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Abstract

With neurodevelopmental outcome of very low birthweight (VLBW) infants being adversely affected by inadequate nutrition during the first few weeks of life, there is an urgent need for more specific nutritional data on the sick VLBW ventilator dependent infant. The development of a new mass spectrometry gas analysis indirect calorimetry system which is non-invasive and can operate over several hours or days is described. Technical evaluation of each of the components of the system indicates a total random error of <5%. Systematic error was determined using gas infusions which simulated carbon dioxide production and oxygen consumption. The relative error in the measurement of carbon dioxide production was ≤1·5% (coefficient of variation (CV) 6·0%)) with carbon dioxide infusion rates ranging from 3·86 to 13·98 ml/min. The relative error in oxygen 'consumption' was ≤4·3% (CV 2·8%) for infusions of oxygen at rates of 7·5 to 14·80 ml/min. With nitrogen infusions simulating oxygen consumptions of 2·0 and 5·5 ml/min the relative error in the calculated nitrogen infusion was 1·5% (CV 4·1%) and 1·4% (CV 5·7%) respectively. Clinical studies on 10 infants demonstrated a mean energy expenditure of 161·7 kJ/kg/day and a respiratory quotient in excess of 1·0. The energy expenditure of ventilated VLBW infants may be less than previously indicated and the energy mix and nitrogen content of parenteral nutrition regimens recommended for these infants may be inappropriate.

Nearly 1% of all infants have a birth weight of less than 1500 g.[1] Although the mortality of this group has greatly diminished in recent years, there is still significant morbidity.[2] More than 60% of these very low birthweight (VLBW) babies suffer from respiratory distress syndrome and require artificial ventilation,[3] the duration of which may be prolonged if the infant develops chronic lung disease. There has been recent concern that inadequate nutrition during this period may not only have a major effect on physical growth of the VLBW baby but may also significantly influence neurodevelopmental outcome.[4 5]

To date, interest in the nutritional status and management of the VLBW baby has concentrated on healthy growing infants, their energy expenditure and nutritional balance being estimated while receiving different feeding regimens.[6] Indirect calorimetry has been the method of choice as it is practicable and accurate for the spontaneously breathing infant. This method provides an estimate of oxygen consumption and carbon dioxide production from which the respiratory quotient (RQ) can be calculated.[7] If simultaneous measurement of urinary nitrogen is made, fat, carbohydrate, and protein utilisation can be calculated.[8] From these studies on healthy premature infants it has been suggested that the total energy intake for enterally fed infants should be in the region of 462–672 kJ/kg/day,[9] and 252–336 kJ/kg/day for infants receiving parenteral nutrition.[10]

It cannot be assumed that this data is meaningful for the sick ventilator dependent infant. The overall work of breathing in these infants will be influenced by the contribution of ventilator support, the frequency of spontaneous respirations, and the compliance of the lungs. In adults, oxygen consumption is increased in trauma and sepsis,[11] both of which are frequently present in sick infants. In healthy premature infants, 15–20% of energy expenditure may be due to spontaneous activity[9]; this is likely to be reduced in the sick and the more premature infant. The overall effect of all of these factors on total energy expenditure in sick ventilated infants is at present unknown.

The lack of calorimetry data on sick ventilator dependent infants is primarily related to the practice of using continuous flow ventilators for neonatal ventilation. These ventilators provide a continuous flow of oxygenated air across the proximal end of the endotracheal tube, thus allowing the inhalation of fresh gas if spontaneous respirations are present. With the continuous gas flows being in the region of 6–8 l/min, and the volume of oxygen consumed and carbon dioxide produced by the infant being only several ml/min, measurement of differences in gas concentrations between inspiratory and expiratory circuits requires a system of considerable accuracy and precision, particularly if the inspiratory oxygen concentration is high. An additional requirement of such a system is the ability to operate over several hours and to allow routine medical and nursing care of the infant to continue unhindered.

These criteria have been taken into consideration during the development of an indirect calorimetry system designed for use in ventilator dependent infants. This paper describes the system and reports the results of technical and clinical evaluation.

The indirect calorimetry system

The system, which is computer driven, consists of a respiratory mass spectrometer, a mesh pneumotachometer with differential transducer, a three way electromagnetic valve, and minor modifications to normal ventilator circuitry (figure). The principle is similar to previously reported open circuit techniques in that samples of gas are drawn from the inspiratory and expiratory circuits and the oxygen consumption and carbon dioxide production are calculated from the product of the volume of gas passing through the ventilator circuit and the changes in oxygen and carbon dioxide occurring between the two circuits. The data from the mass spectrometer and the pneumotachometer are received by the microcomputer, and oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), respiratory quotient (RQ), and energy expenditure (EE) are calculated using the Weir equations[7]:

$\dot{V}O_2$ ml/min=$\dot{V}E$ ml/min (FIO_2-FEO_2)
$\dot{V}CO_2$ ml/min=$\dot{V}E$ ml/min ($FECO_2-FICO_2$)
Energy expenditure (kJ/min) = [3·9 ×$\dot{V}O_2$ (l/min)+ 1·1×$\dot{V}CO_2$ (l/min)]×4·2

where $\dot{V}E$ is minute ventilation, FIO_2 and FEO_2 are fractional inspired and expired oxygen, and $FECO_2$, and $FICO_2$ are fractional expired and inspired carbon dioxide.

Each of the measured parameters is graphically displayed in real time on the computer screen. If urine is collected during the study, this enables the measurement of urinary nitrogen which will allow the determination of the non-protein RQ, fat, carbohydrate and protein utilisation,[8] and additional nutritional parameters, which can be calculated by the dedicated software.

Methods

TECHNICAL EVALUATION

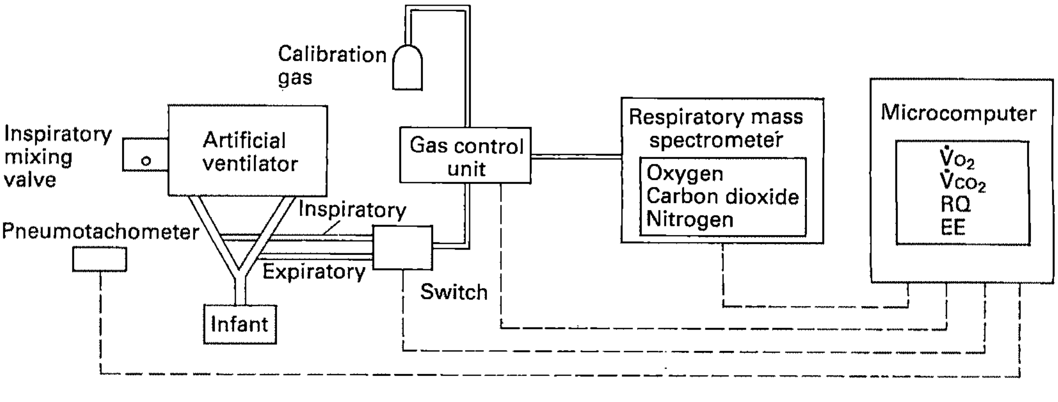
The evaluation of the system was first approached by determining the errors of each of the components of the system. The calculations stated above include three measured values: the volume of gas flow and the concentrations of oxygen and carbon dioxide in the inspiratory and expiratory circuits. The minimum expected error was therefore the sum of the errors sustained in obtaining these specific measurements. Other potential areas of error were the gas sampling process and the effects of varying pressure, humidity, and temperature within the ventilator circuitry. It was also recognised that without a perfect 'gold standard' against which the system could be compared, a component of the systematic error could be due to error in measurement of the gold standard—in this case gas infusion studies—rather than the calorimetry system.

Infant ventilator

The infants were ventilated with a continuous flow, time cycled infant ventilator (Sechrist Model IV-100B). Depending on the compressible volume of the circuit and the humidifier, a flow rate of 6–8 l/min is usually required to achieve adequate peak pressure and pressure rise time. Initial analysis of gases sampled from the inspiratory and expiratory circuits demonstrated that there was contamination of the gas samples taken from the expiratory circuit. This was found to be due to a low pressure flow of gas which, occurring during the exhalation phase, passed from the fluidic control system to the pressure alarm system via the pressure sense line, and this line connected with the patient attachment at the proximal end of the expiratory circuit. This flow of gas was not essential for normal ventilator performance, and after discussion with the distributing company (EME, Brighton) this gas flow was disconnected.

Flow measurements

The flow through the ventilator circuit was measured by a mesh type pneumotachometer which was situated in the inspiratory circuit, proximal to the humidifier. The pneumotachometer was connected to a differential pressure transducer (Airspec), which had an output of 5 V for 12 l/min and linearisation over a range of 0–12 l/min. Calibration of the pneumotachometer was undertaken using a calibrated syringe and a previously described computerised method which determines the conductance characteristics of the flowmeter.[12] The conductance values of the pneumotachometer correspond to pressure values which are determined by a weighted averaging technique, following multiple strokes of the precision calibrated syringe. The conductance values allow the measured differential pressures to be converted point to point into flows. The precision of repeated calibrations was ±0·3% of the syringe



Schematic flow-diagram of indirect calorimetry for ventilator dependent infants.

volume using a 50 stroke calibration process. The accuracy of measured volumes was shown to be within ±0·5% after a 100 stroke calibration process. Calibration was performed using room air, and as the pneumotachometer is situated proximal to the humidifier, the effect of the difference in temperature, humidity, and pressure from ventilation gas was considered to be minimal.

Connections

Gas samples of approximately 100 ml/min were obtained through access points within the inspiratory and expiratory circuits and transmitted through capillaries to a standard miniature three way electromagnetic valve (Airspec), which was operated by computer control. The sampling times for inspiratory and expiratory gas can be individually programmed and in the reported clinical studies the inspiratory time was 12 seconds and expiratory time 38 seconds. The valve directed the sample gas through a single capillary to the mass spectrometer. With both inspiratory and expiratory samples being fed in turn to the mass spectrometer through a common capillary, the effects of pressure sensitivity on the analyses were removed.

Mass spectrometer

Paramagnetic oxygen analysers and infrared carbon dioxide analysers require gas samples to pass through a drying chamber before analysis. This produces a significant delay in the response time, and therefore accurate synchronisation of the time of analysis with the collection time is necessary. This potential error can be avoided by measuring oxygen and carbon dioxide by mass spectrometry. With this method the gases are measured directly and the response time is such that the measurements can be considered immediate and simultaneous. In this system a quadrupole mass spectrometer, (Airspec MGA 2000) was used. Factory evaluation of this instrument showed that reproducibility was better than 1% of value, drift was less than 1% in 24 hours, and linearity was better than 1% for uncorrected data. This instrument has a measurement resolution of 12 bits for 10 V, and in the slow mode each gas is analysed every 20 ms with each data acquisition being the average of 256 measurements. The procedure of tuning and calibration of gases can be undertaken manually, or remotely by computer control. In this application the mass spectrometer was tuned to measure the concentration of oxygen, carbon dioxide, argon, and nitrogen.

Systematic error

Initial validation studies of the complete system were undertaken using a dummy lung configuration. The dummy lung was a 0·5 litre rebreathing bag (M and IE Dentsply) and this was ventilated with settings similar to those required by an infant with moderately severe respiratory disease—rate 40/min, F_{IO_2} 40%, and inspiratory and expiratory pressures 20/4 cm H_2O. The aims of this part of the evaluation were to determine drifts in measurement of oxygen and carbon dioxide concentration over time, and to confirm zero gas exchange with this non-breathing system. Over the 24 hour study period drifts in oxygen concentration of ±0·5% were recorded and the carbon dioxide concentration remained within ±0·02%. To counteract the effect of possible drift on the calculations, the values taken for inspiratory gas concentrations were the mean of the measurements taken before and after expiratory sample. With this modification, the mean $\dot{V}O_2$ and $\dot{V}CO_2$ measured using the dummy lung configuration over 24 hours was 0·0 (±0·1).

To assess the ability of the system to measure accurately the gas exchange, gas infusion studies were designed to simulate the levels of carbon dioxide production and oxygen consumption that are likely to occur in sick premature infants. The ventilator settings during the infusion studies were as described above. In each case the relevant test gas was infused into the inspiratory circuit by a peristaltic infusion pump P-3 (Pharmacia). The peristaltic pump was used in preference to a continuous flowmeter because the former emitted the gases in pulses and was therefore more accurately simulating the intermittent nature of respiration. The flow rate of the pump was measured at regular intervals throughout each study period by infusing the gas into a previously calibrated U shaped water manometer and, from the volume of water displaced over a measured period of time, the flow rate was calculated. The time periods were measured by a hand held stopwatch with a precision of 0·01 seconds. The random error of the time measurement was assessed by recording repeated time measurements for the same displacement of water (7 ml). The mean (SD) of 20 measurements was 14·92 (0·11) seconds with the coefficient of variation (CV) of <0·75%. The method of timing was therefore sufficiently precise.

The use of the water manometer provided the additional advantage of allowing the measurement of the gas flow to be performed against a pressure similar to that experienced when infusing into the ventilator circuit—that is 4–20 cm H_2O. Saturation of the water with the infused gases was considered, but thought unlikely to occur, as the duration of infusion of gas through the manometer was always less than 60 seconds. However, this was investigated by infusing oxygen, carbon dioxide, and nitrogen over longer periods of time in order to identify changes in calculated flow rate. The flow rates were unchanged with time and the effect of any saturation was therefore considered to be negligible.

The results of the gas infusion studies are shown in table 1. The carbon dioxide infusion ($\dot{W}CO_2$) directly simulates carbon dioxide production ($\dot{V}CO_2$). Nitrogen infusions simulate oxygen consumption by creating an oxygen difference, which in gas exchange formulas is equivalent to oxygen consumption ($\dot{V}O_2$). Using the measurements obtained during the infusion, the volume of nitrogen infused ($\dot{W}N_2$) and 'oxygen consumption' can be calculated.

Table 1 *Gas infusion studies*

Infusion	*Flow in ml/min*	*Measured* $\dot{V}CO_2$ *in ml/min (SD)*	*% CV*	*% Relative error*	*Measured* $\dot{V}O_2$ *in ml/min (SD)*	*% CV*	*% Relative error*	*Calculated nitrogen in ml/min (SD)*	*% CV*	*% Relative error*
Carbon dioxide	3·86	3·80 (0·23)	6·0	−1·5	—	—	—	—	—	—
	9·20	9·0 (0·13)	1·4	−1·2	—	—	—	—	—	—
	13·98	13·83 (0·53)	3·8	−1·1	—	—	—	—	—	—
Oxygen	7·5	—	—	—	(−) 7·8 (0·31)	4·0	4·1	—	—	—
	9·36	—	—	—	(−) 9·7 (0·44)	2·8	4·3	—	—	—
	14·80	—	—	—	(−) 15·10 (0·42)	2·0	2·0	—	—	—
Nitrogen	10·10	—	—	—	1·90 (0·1)	5·3	—	9·95 (0·41)	4·1	−1·5
	14·10	—	—	—	5·45 (0·49)	8·9	—	14·20 (0·82)	5·7	1·4

$$\text{Relative error}=\frac{\text{calculated value}-\text{true value}}{\text{true value}}\times 100\%.$$

Table 2 *Clinical studies on ventilated infants. Values as mean (SD)*

	Biological data				*Ventilation*		*Nutritional intake*		*Calorimetry*			
	Birth weight (g)	*Gestation (weeks)*	*Age (days)*	*Weight (g)*	*Rate/ min*	*%* FIO_2	*Energy intake (kJ/kg/ 24 hours)*	*Protein intake (g/kg/ 24 hours)*	*Energy expenditure (kJ/kg/ 24 hours)*	$\dot{V}O_2$ *(ml/kg/ min)*	$\dot{V}CO_2$ *(ml/kg/ min)*	*RQ*
Total parental nutrition (n=5)	1286 (125)	28·8 (2·0)	5 (0·7)	1126 (159)	30 (20)	32 (6·5)	315 (23)	2·1 (0·6)	177·6 (36)	5·80 (1·10)	6·17 (1·50)	1·07 (0·16)
Intravenous dextrose (n=5)	1862 (522)	30·2 (3·3)	2·4 (1·3)	1843 (593)	41·4 (25)	30·4 (8·8)	194 (11)	—	147·9 (24)	4·66 (0·80)	5·72 (0·80)	1·13 (0·08)

$$\dot{W}N_2=\frac{\dot{V}(FIO_2-FEO_2)}{FEO_2}$$

where $\dot{W}N_2$ is the volume of nitrogen infused, and $\dot{V}$ is flow volume per minute.

$$\dot{V}O_2=(\dot{V}_1\times FIO_2)-(\dot{V}_2\times FEO_2)$$

$\dot{V}_1$ is inspiratory flow volume per minute, and $\dot{V}_2$ is the expiratory flow volume—that is $\dot{V}_1+\dot{W}N_2$.

As a more direct method of measuring small oxygen differences between inspiratory and expiratory samples, oxygen infusions were undertaken. In this test lung configuration the increased oxygen concentration was present in the expiratory sample, producing a measurable 'negative' oxygen consumption, which was calculated as shown above. Each gas infusion was a minimum of 60 min duration (range 60–90 min) and the means, SD and, CV were calculated on a minimum of 40 data points (table 1).

CLINICAL STUDIES

Clinical evaluation was undertaken on 10 preterm ventilated infants and the results are summarised in table 2. The infants have been divided into those receiving total parenteral nutrition and those who were receiving dextrose infusion. The mean energy expenditure of all the infants studied was 161·7 kJ/kg/24 hours, with the lowest measurement of 120·8 kJ/kg/24 hours) being in an infant of 28 weeks' gestation who was paralysed with a muscle relaxant. The mean RQ was greater than 1·0 in both groups.

The possibility of respiratory gases bypassing the endotracheal tube was investigated at the start of each study by placing the capillary adjacent to the nose and the mouth of the infant. If carbon dioxide and/or oxygen were detected then a flow through technique, using a canopy which completely enclosed the infant, was undertaken. The only difference from the ventilator system was that the inspiratory capillary sampled air entering the canopy and the expiratory capillary sampled the air leaving the canopy. This was undertaken at the start and finish of the studies, and the mean of the results included in the overall calculations. The extratracheal $\dot{V}O_2$ ranged from −0·1 to +0·2 ml/min and $\dot{V}CO_2$ from 0·0 to +0·2 ml/min. In 5/10 infants there was no bypassing of the endotracheal tube.

Discussion

An indirect calorimetry system for measuring energy expenditure and nutrient utilisation in sick ventilator dependent infants is described. Evaluation of the system showed there was no significant bias, and the instruments used were precise and accurate. Total system error during the worst test conditions was <5·0%. The inspiratory oxygen concentration during the studies was 40% and therefore the ratio of signal to noise very small during the studies with the low oxygen flows, but even in those conditions a relative error of 4% and coefficient of variation 4% would indicate that the system has adequate precision and accuracy to be used in the sickest infants.

The principle objectives of the system have been achieved in that it is non-invasive, compatible with continuous flow infant ventilators, and operates without inconveniencing medical or nursing care. Studies of energy expenditure can continue for 24 hours or longer and can start from the moment the infant is placed on the ventilator.

The rapid response time of the analyses and the real time graphic display enables the acute and chronic effects of procedures and medications on energy expenditure and nutrient utilisation to be studied. The management of the sick premature infant involves a number of interventions which are likely to influence the energy balance and nutritional status of the infant—in particular, the administration of surfactant, dexamethasone, and transfusion of blood.

Failure to capture all of the expired respiratory gases is a potential source of error with this method. It is also possible that ventilator gas may leak from the distal end of the endotracheal tube without entering the infant's lower respiratory tract, thus producing a falsely high measurement for oxygen consumption. Leakages are less likely in the more premature infants and those infants who have had an endotracheal tube in situ for a short time. Our findings were similar to those of Lucas and colleagues who found that bypassing of the endotracheal tube occurred in less than half the infants studied and was not more than 0·2 ml/min for carbon dioxide.[13] In our studies we detected that the maximum leakage for both oxygen and carbon dioxide was 0·2 ml/min. The contribution of the skin to gas exchange has previously been reported as being up to 15% in the smallest infants.[14] For these reasons we introduced our canopy method in which the whole infant was enclosed and the results obtained are thought to reflect all extratracheal gaseous exchange. Ideally, the canopy method should run simultaneously with sampling from the ventilator circuits and this may be possible with the aid of a multiplex valve, but this has yet to be tested. Modified face masks have been used to collect intratracheal and extratracheal gases,[15] but the placement of a mask on the face of an infant interferes with normal nursing care, and because of its invasiveness may have an independent influence on the results obtained.

The clinical studies confirmed that the system did not affect the respiratory management of the infant, and normal nursing and medical procedures were able to be undertaken. Preliminary results indicate that energy expenditure may be lower than previously suspected. This is likely to be due to the decrease in the work of breathing and also because of the reduced activity of the sick premature infant. More formal studies are now in progress to confirm these findings.

The respiratory quotient was generally greater than 1·0 and was particularly high in some infants receiving intravenous dextrose alone. It has been demonstrated in adults that a high intravenous carbohydrate intake results in carbohydrate being converted to fat, and this process results in a considerable increase in carbon dioxide production.[16] In order to eliminate this additional carbon dioxide, infants are likely to require increased ventilator support: in our study the infant with the highest RQ was being ventilated with air because of persistent carbon dioxide retention. Thus, a more appropriate parenteral nutrition regimen may not only improve the growth and development of the infant but also reduce the degree and duration of ventilator support.

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Positive end expiratory pressure in acute and chronic respiratory distress

A Greenough, V Chan, M F Hird

Abstract

The optimum level of positive end expiratory pressure (PEEP) was determined in 16 infants with respiratory distress syndrome (median gestational age 29 weeks, median postnatal age 1 day) and in 16 infants with chronic respiratory distress (median gestational age 25 weeks, median postnatal age 15 days). All infants were studied at a PEEP sequence of 3, 0, 3, 6, and 3 cm H_2O, all other ventilator parameters being kept constant. Each PEEP level was maintained for 20 minutes and at the end of each period arterial blood gas was checked. During acute respiratory distress syndrome there were no significant changes in oxygenation but arterial carbon dioxide tension ($Paco_2$) significantly decreased from a mean of 4·93 kPa at 3 cm H_2O to 4·40 kPa at 0 cm H_2O and increased to a mean of 5·87 kPa at 6 cm H_2O. In the infants with chronic respiratory distress, oxygenation fell from a mean of 8·66 kPa at 3 cm H_2O to 6·40 kPa at 0 cm H_2O and improved at 6 cm H_2O to a mean of 10·50 kPa. There were no significant changes in $Paco_2$. We conclude that addition of PEEP, up to 6 cm H_2O, may be useful even after the first week of life. High levels of PEEP, however, have previously been reported, in certain infants, to result in circulatory disturbance. It is therefore important to assess the use of 6 cm H_2O PEEP in a controlled study of longer term clinical outcome.

During acute respiratory distress syndrome addition of positive end expiratory pressure (PEEP) during mechanical ventilation is useful.[1] Addition of PEEP increases mean airway pressure improving oxygenation,[2 3] and it also results in surfactant conservation.[4] In severe respiratory distress syndrome levels of PEEP of up to 10 cm H_2O have been recommended.[5] Such studies, however, were performed on infants with severe respiratory distress syndrome.[1–3 5]

Many of the present population of preterm infants do not suffer from severe respiratory failure. It has been suggested that among this group of infants even relatively low levels of PEEP may cause alveolar overdistension, with reduced compliance and carbon dioxide retention.[6] Those results, however, may be explained by the inclusion of relatively mature infants (mean gestational age 32 weeks). Investigation of very immature infants, whose respiratory distress would be expected to be more severe, may still demonstrate that addition of PEEP during mechanical ventilation may be beneficial. It is also difficult to predict the optimum PEEP levels in infants remaining ventilated beyond the first week of life as at this age airways resistance is high,[7] yet surfactant abnormalities may coexist.[8] The aim of this study was to determine the optimum level of PEEP during mechanical ventilation of very preterm infants with acute respiratory distress and to see if this differed for infants ventilated beyond the first week of life.

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Methods

Consecutive infants were recruited into the study who had been ventilated either for less than four days (acute respiratory distress) or at least 14 days (chronic respiratory distress). Infants with congenital or nosocomial pneumonia were excluded from the study.

Infants were all studied at the same sequence of PEEP levels, 3, 0, 3, 6, and 3 cm H_2O (3 cm H_2O being the baseline level), each level being maintained for 20 minutes. The three levels of PEEP were chosen as they all had previously been used on our unit during routine clinical management of infants with respiratory distress. Peak inflating pressure, inspiratory:expiratory ratio, ventilator rate, and inspired oxygen concentration were kept constant at each PEEP level.

Throughout the PEEP sequence infants were continuously monitored by an intra-arterial Searle electrode or a transcutaneous oxygen electrode. If this monitoring demonstrated the arterial oxygen tension (Pao_2) to fall below 5·33 kPa the infant was immediately returned to the baseline PEEP level. The inspired oxygen concentration was increased after checking the arterial blood gas, and the study then abandoned.

At the start of the study and at the end of each 20 minute period, arterial blood gases were checked from the indwelling catheter sited for clinical purposes. Pao_2 and arterial carbondioxide tension ($Paco_2$) values at 0 and 6 cm H_2O were then compared with the mean value obtained at the three periods at the baseline of 3 cm H_2O of PEEP.

TRIAL SIZE

Recruitment of 16 infants into each group gave us the possibility of detecting a change of 2·13 kPa in oxygenation and 1·07 kPa in $Paco_2$ between PEEP levels in the infants with acute respiratory distress with 80% power at the 5% level, and a change of 2·00 kPa in oxygenation and 1·33 kPa in $Paco_2$ in the infants with chronic respiratory distress with 85% power at the 5% level.

STATISTICAL ANALYSIS

To assess if differences at different PEEP levels were significant a Student's *t* test was used. The confidence intervals were calculated with the appropriate p value from the standard error of the difference between the different PEEP levels. To assess if differences between groups were significant a Wilcoxon rank sum test or Fisher's exact test was used.

Patients

Sixteen infants were studied in the first four days of life, all of whom were ventilated for respiratory distress syndrome. Their median gestational age was 29 weeks (range 23–33), postnatal age was 1 day (0·5–4), and birth weight 1054 g (510–2110). The median inspired oxygen concentration of these patients was 33% (range 21–95) and their peak inspiratory pressure was 16 cm H_2O (range 14–27).

Another group of 16 infants were studied: they had been ventilated initially for respiratory distress syndrome but then remained fully ventilator dependent (rates ≥30 breaths/minute) beyond 1 week of age. Their median gestational age was 25 weeks (range 24–29), birth weight 806 g (range 600–1140), and postnatal age 15 days (range 12·5–31). Only two infants were older than 3 weeks of age, but both were recruited at the beginning of the study. The median inspired oxygen concentration of the 16 patients was 40% (range 28–80) and peak pressure was 17 cm H_2O (range 14–24). At the time of entry into the study five infants were receiving dexamethasone to facilitate weaning from mechanical ventilation. When infants were older than 2 weeks of age they were entered into the study on the first occasion a chest radiograph was taken for clinical purposes. The chest radiograph was used to determine the nature of the infant's chronic respiratory distress. The radiographs of nine infants demonstrated areas of collapse and consolidation. One infant had resolving pulmonary interstitial emphysema and two others had evolving bronchopulmonary dysplasia with overinflated lungs. The remaining four infants all had evidence of heart failure and were the only four infants who had a patent ductus arteriosus at the time of study.

Ethical permission for this study was granted by the King's College Hospital ethical committee.

Results

One infant with chronic respiratory distress did not complete the 20 minute period at 0 cm H_2O. After 10 minutes the continuous monitoring indicated the PaO_2 had fallen below 5·33 kPa, an arterial blood gas reading was taken which indicated the PaO_2 was in fact 3·20 kPa, so the infant was immediately returned to 3 cm H_2O PEEP. No other infant showed such an appreciable deterioration in blood gases at any PEEP level.

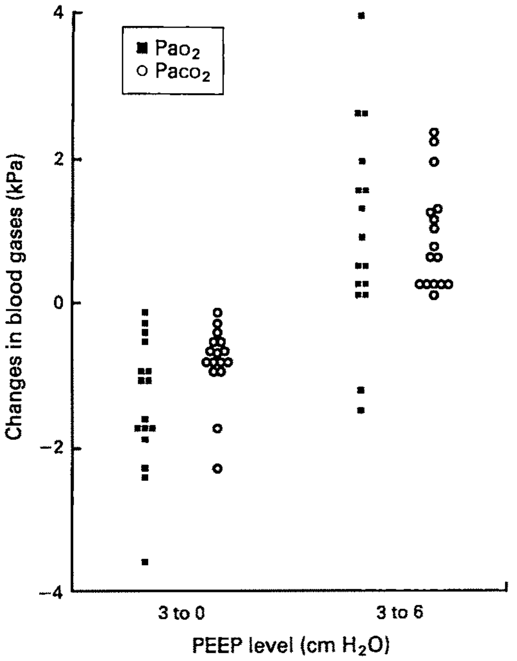

Figure 1 Changes in PaO_2 and $PaCO_2$ at different PEEP levels in acute respiratory distress syndrome. Individual data are displayed as the change in PaO_2 or $PaCO_2$ from the baseline.

Respiratory distress in the two groups of infants. Results are mean (SE of difference from baseline) in kPa

	PEEP level (cm H_2O)				
	3	*0*	*3*	*6*	*3*
Acute respiratory distress:					
PaO_2	9·27	7·89	9·75	10·58	9·76
		(0·91)		(1·44)	
$PaCO_2$	5·19	4·36	4·93	5·87	4·94
		(0·53)		(0·75)	
Chronic respiratory distress:					
PaO_2	8·83	6·46	8·62	10·56	8·27
		(1·32)		(2·03)	
$PaCO_2$	6·35	6·35	6·21	6·69	6·13
		(0·69)		(0·31)	

ACUTE RESPIRATORY DISTRESS

In the 16 infants overall there was no significant change in oxygenation at either 0 or 6 cm H_2O compared with baseline (fig 1, table). For PaO_2, the 95% confidence intervals of the difference of the means of 3 and 0 cm H_2O PEEP were 0·10 to 2·81 kPa and of 3 and 6 cm H_2O PEEP were −0·44 to 2·27 kPa. $PaCO_2$ was significantly lower at 0 cm H_2O ($p<0·05$) and significantly higher at 6 cm H_2O ($p<0·01$) compared with baseline. For $PaCO_2$, the 95% confidence intervals of the difference of the means of 3 and 0 cm H_2O PEEP were 0·12 to 1·56 kPa and of 3 and 6 cm H_2O PEEP were 0·10 to 2·00 kPa.

Fourteen of the 16 infants showed similar trends in blood gases with changes in the PEEP levels; that is, an increase in both PaO_2 and $PaCO_2$ at 6 cm H_2O and a decrease in PaO_2 and $PaCO_2$ at 0 cm H_2O, but the changes were small. Two infants, however, although showing a similar trend in $PaCO_2$ to the rest of the study group had a deterioration in PaO_2 at both 0 and 6 cm H_2O. These two infants did not differ significantly in either postnatal age or baseline blood gas values from the rest of the group.

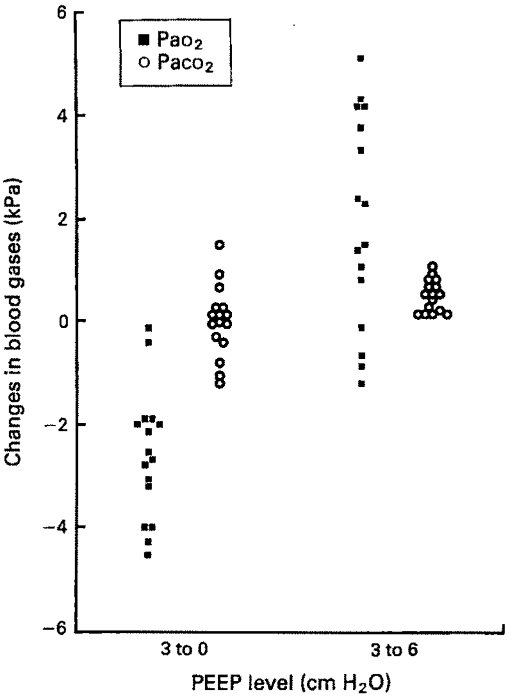

Figure 2 Changes in Pao_2 and $Paco_2$ at different PEEP levels in chronic respiratory distress syndrome. Individual data are displayed as the change in Pao_2 or $Paco_2$ from the baseline.

CHRONIC RESPIRATORY DISTRESS

In the group overall the trends in changes in Pao_2 were similar to those seen in the infants with acute respiratory distress, but they were much larger (fig 2) and were significant at both 0 cm H_2O ($p<0{\cdot}01$) and 6 cm H_2O ($p<0{\cdot}01$). For Pao_2, the 95% confidence intervals of the difference of the means of 0 and 3 cm H_2O were 1·25 to 3·50 kPa and of 3 and 6 cm H_2O were 0·31 to 3·57 kPa. There was, however, no significant change in $Paco_2$ with changes in PEEP (table). For $Paco_2$ the 95% confidence intervals for the difference in the means of 0 and 3 cm H_2O PEEP were −0·88 to 0·89 kPa and of 3 and 6 cm H_2O were −0·39 to 1·48 kPa.

Twelve of the 16 infants showed similar trends in blood gases with changes in PEEP levels; that is, an increase in Pao_2 and $Paco_2$ at 6 cm H_2O and decrease in Pao_2 at 0 cm H_2O. Four infants had similar changes in $Paco_2$ values to the rest of the group and impairment of oxygenation at 0 cm H_2O, but showed a reduction in Pao_2 at 6 cm H_2O compared with baseline. These four infants did not differ significantly from the rest of the group in either postnatal age or baseline blood gases, but did have a different chest radiograph appearance to the other 12 infants. These four infants were the only ones whose chest radiograph appearance was compatible with heart failure and had a patent ductus arteriosus at the time of study. There was no significant difference in the oxygen requirements or peak inspiratory pressure in the four infants and the remainder of the group.

Discussion

We felt it important to perform exactly the same protocol in the two groups as, by allowing direct comparison, this facilitated determination of differences in the effect of PEEP with increasing postnatal age. Infants were left at each PEEP level for 20 minutes and as we assessed the effect by measuring arterial blood gases rather than transcutaneous values,[6] we felt this was sufficient time for stabilisation at the new PEEP level. To minimise the effect of a trend with increasing time the infants were always returned to the baseline 3 cm H_2O immediately after the period at the experimental PEEP level.

These results demonstrate that increasing postnatal age did not affect the response to increasing PEEP levels as determined by trends in changes in oxygenation. In the infants with chronic respiratory distress oxygenation was significantly improved at 6 cm H_2O and impaired at 0 cm H_2O. Similar trends were seen in the infants with acute respiratory distress but the changes were very small. Similar differences in response have been demonstrated in other respiratory diagnoses. Field *et al* noted a much greater improvement in oxygenation among infants with apnoea of prematurity than in those with respiratory distress syndrome, the former group having the lower compliance.[6] Our infants with chronic respiratory distress were ventilated at similar pressures to those with acute respiratory distress but had higher $Paco_2$, suggesting that they did have lower lung compliance. This seems likely as their median gestational age was 25 weeks compared with 29 weeks of the acute respiratory distress group.

Four of the 16 infants with chronic respiratory distress did not show an improvement in oxygenation at 6 cm H_2O. Interestingly, these four infants were the only ones who had a chest radiograph appearance compatible with heart failure and had a patent ductus arteriosus at the time of study. Our results, therefore, seem surprising as the presence of a patent ductus arteriosus associated with heart failure might reduce lung compliance and thus a higher level of PEEP would be predicted to be more appropriate. The similar peak inspiratory pressures and inspired oxygen concentration in these infants compared with the rest of the group, however, suggest similar degrees of lung function impairment. Addition of PEEP in this group, however, was still clearly useful, as oxygenation deteriorated when the PEEP level was changed from 3 to 0 cm H_2O. Our results may indicate that the optimum level of PEEP in such infants is 3 cm H_2O, but as only four infants were involved we need to assess if this response is consistent in greater numbers of infants.

Increasing PEEP while maintaining peak inspiratory pressure constant is likely to reduce both delivered volume and minute volume. This reduction in delivered volume may partially explain the significant increase in $Paco_2$ values at higher PEEP levels seen among our infants with acute respiratory distress. The effect of carbon dioxide retention was greater in this study than that of Field *et al* and the likely explanation is that we used higher PEEP levels.[6] No significant effect on carbon dioxide values was seen in the infants with chronic respiratory distress. There was, however, an upward trend in $Paco_2$ values with increased PEEP and our results may have failed to reach significance due to a small sample size. It is also possible that a further mechanism might operate to alter $Paco_2$ values with changing levels of PEEP. Richardson *et al* found that, although changes in Pao_2 did not correlate well with change in functional residual capacity, in those infants in whom an impairment of oxygenation was associated with an increase in functional residual capacity there was always an accompanying increase in $Paco_2$—indicating alveolar overdistension and decreased alveolar ventilation.[5] Thus our results may imply that the infants with acute respiratory distress had more compliant lungs than those with chronic respiratory distress and were thus more susceptible to increasing levels of PEEP causing alveolar overdistension and carbon dioxide retention.

It might have been expected that increasing PEEP levels in infants with chronic respiratory distress would also cause alveolar overdistension and carbon dioxide retention. This sequela is most likely to occur in infants with hyperinflated lungs which contain cystic areas typical of Northway type IV bronchopulmonary dysplasia. Infants with this chest radiograph appearance, however, represent the minority of infants ventilated beyond the first week of life[9] and indeed were only two of our 16 subjects consecutively recruited into the study. The majority of infants who require respiratory support after the first week of life suffer from type I chronic lung disease[10] and are represented by our group of nine infants whose chest radiograph showed evidence of areas of collapse. Such infants have underexpanded areas of lung which could be recruited by increasing PEEP without causing overdistension and carbon dioxide retention.

These results demonstrate that increasing the PEEP level continues to have an advantageous effect even after the first week of life, and that in chronic respiratory distress PEEP levels as high as 6 cm H_2O can improve oxygenation without significant carbon dioxide retention; this finding is important. The strategy of increasing PEEP levels would allow maintenance of arterial blood gases at lower peak pressures during subsequent ventilation which might reduce further lung damage. It must be stressed, however, that high levels of PEEP can be associated with circulatory disturbance. In surfactant depleted rabbit's lungs, although adequate arterial oxygenation can be maintained with PEEP at 10 cm H_2O, the associated circulatory impairment, as evidenced by reduced arterial pressure and aortic blood flow, results in inadequate oxygen delivery.[11] In another animal model[12] increasing PEEP from 5 to 15 cm H_2O resulted in a reduction in left ventricular stroke volume, which was due to impaired left ventricular filling rather than a concomitant depression of myocardial contractility. In the present study no such adverse effects were experienced but the maximum PEEP level used was lower than in the other studies. These data, however, stress the importance of proceeding to assess the use of 6 cm H_2O in infants with chronic respiratory distress in controlled studies of longer term clinical outcome.

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Randomised trial of nutrition for preterm infants after discharge

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Abstract

In a randomised double blind trial, the effect on growth and clinical status of a nutrient enriched 'post-discharge' milk formula versus a standard term formula, was compared in 32 exclusively bottle fed preterm infants. The formulas were used as the sole milk intake up to a postnatal age of 9 months.

Significant increases in linear growth and weight gain were observed in the infants who received the enriched diet. There were no differences in vomiting, posseting, or bowel habit between the groups. Formula volumes ingested were similar between diet groups, indicating that the difference in formula composition did not affect the infants' regulation of intake.

These preliminary data suggest that there is a role for specially designed formulas for preterm infants after discharge from hospital.

There has been increasing recognition that preterm infants have special nutrient needs.[1–3] Somatic growth, brain growth, and overall nutrient accretion rates in the third trimester substantially exceed those of the infant born at term.[4] Premature delivery interrupts these processes, and the preterm infant begins postnatal life with comparatively low body stores, particularly of fat, bone minerals, trace metals, and some vitamins. Modern dietary regimens, for instance those employing formulas that have been designed to meet the special increased needs of preterm infants, may confer major benefits for long term growth and developmental attainment in early childhood.[5–7]

The focus of attention in this field, however, has been almost exclusively on hospital based nutritional management. Yet preterm infants are frequently discharged home at a body weight of 1800–2000 g, little over half that of a newborn full term baby. It is not uncommon for both length and weight to be below the 3rd centile at this time. Moreover, unpublished data from our multicentre studies show that, as a population, preterm infants are still growth retarded at 9 and 18 months.

Despite the intensive nutritional management provided during hospitalisation, these infants are discharged home on diets suitable for healthy term babies when they have frequently fulfilled the most stringent criteria for failure to thrive. It seems reasonable to speculate that babies born preterm would continue to benefit from special nutritional attention for the early months after discharge from hospital and possibly throughout infancy.

We have therefore undertaken a randomised, double blind prospective study of the effects on growth and development of a specially designed enriched 'post-discharge' formula, compared with the currently available term formula diet, in a group of preterm infants whose mothers had elected to bottle feed. Our findings on growth, formula intake, and feed tolerance up to 9 months post-term are reported here.

Subjects and methods

We recruited 32 preterm infants before discharge home after they had received neonatal intensive care. These infants weighed less than 1850 g at birth. The criteria for inclusion were that they had been formula fed rather than breast milk fed during the hospital stay, were free of congenital malformations and diseases likely to influence growth and neurodevelopment, weighed less than 3 kg at the time of entry to the study, and were aged less than 100 days. After informed parental consent had been obtained, infants were randomised to receive either a standard 'term' formula (Farley's Oster Milk, Crookes Health Care Ltd), or a specially designed 'follow-on preterm formula' (Farley's Premcare, manufactured for us by Crookes Health Care Ltd; see table 1 for compositional details), both in ready to feed form. Before

Table 1 Composition of nutrient enriched post-discharge milk formula

	Per 100 ml	*Per 100 kcal†*
Protein (g)	1·85*	2·6
Fat (g)	4·0	5·5
Carbohydrate (g)	7·3	10·1
Calcium (mg)	70	97
Chloride (mg)	45	63
Copper (μg)	57	80
Iodine (μg)	4·5	6·3
Iron (μg)	650	900
Magnesium (mg)	5·2	7·2
Manganese (μg)	5	7
Phosphorus (mg)	35	49
Potassium (mg)	78	110
Sodium (mg)	22	31
Zinc (μg)	600	840
Vitamin A (μg)	100	139
Vitamin B-1 (μg)	95	132
Vitamin B-2 (μg)	100	139
Vitamin B-6 (μg)	80	111
Vitamin B-12 (μg)	0·2	0·3
Biotin (μg)	1·1	1·5
Folate (μg)	25	35
Niacin (μg)	1000	1388
Pantothenate (μg)	400	555
Vitamin C (mg)	15	21
Vitamin D (μg)	1·3	1·8
Vitamin E (mg)	1·5	2·1
Vitamin K (μg)	6·0	8·3
Taurine (mg)	5·1	7·1
Carnitine (mg)	1·1	1·5
Energy (kcal†)	72	100
Inositol (mg)	3·2	4·4
Choline (mg)	5·1	7·0

*Casein:whey ratio 40:60. †100 kcal=418 kJ.

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Table 2 Demographic, clinical, and anthropometric characteristics of study groups (data are means (SD) unless otherwise stated)

	Standard term formula (n=15)	*Follow-on preterm formula (n=16)*
Gestation (weeks)	31·7 (1·9)	30·7 (1·7)
Birth weight (g)	1436 (227)	1513 (173)
Males:females	8:7	7:9
No of infants ventilated		
>1 day	6	8
>7 days	0	1
Median No days on intravenous nutrition (interquartile range)	4 (2–8)	5 (3–10)
Postmenstrual age at trial entry (weeks)	37 (2)	37 (2)
Anthropometry at trial entry:		
Weight (g)	2383 (221)	2401 (343)
Length (cm)	46·0 (1·4)	46·3 (2·2)
Head circumference (cm)	33·3 (1·0)	33·2 (1·2)
Triceps skinfold (mm)	5·0 (1·1)	4·7 (1·1)
Subscapular skinfold (mm)	4·5 (0·6)	4·8 (1·1)

*Partial or complete.

Table 3 Milk volume intake at corrected postnatal ages. Data are mean (SD) in litres

	0–3 Months	*>3–6 Months*	*>6–9 months*
Standard term formula (n=15)	73·4 (13·5)	69·4 (15·4)	75·1 (32·0)
Follow-on formula (n=16)	71·6 (14·9)	69·8 (12·2)	65·6 (23·9)

randomisation, all the infants had been in the Rosie Maternity Hospital neonatal intensive care unit, and had had intensive data collection undertaken from birth.

The infants were started on the assigned diet while still in hospital; clinical data, together with mean postmenstrual age and anthropometric data at trial entry are given in table 2.

After discharge from hospital, a research nurse (FJK) visited each infant fortnightly to record anthropometry and clinical data. Weight was measured to the nearest 10 g using a Sartorius MP electronic balance; length was measured using a horizontal stadiometer to the next succeeding 1 mm; occipitofrontal circumference was measured to the next succeeding 1 mm using a paper tape measure; skinfold thicknesses—triceps and subscapular—were measured to the nearest 0·1 mm using Harpenden calipers.

At each visit, further supplies of milk were delivered. Boxes were weighed before delivery, and the parents instructed to replace capped empty or partially emptied bottles in the boxes after use. Volume intake over the two week period was calculated by subtracting the weights of used or partly used boxes of milk from their full weights (see table 3 for volume intake details).

The infants received the assigned diet, either as a sole source of nutrition or in conjunction with other foods until 9 months corrected postnatal age.

Student's *t* test and χ^2 analyses were used to compare the two groups at specific corrected postnatal ages.

Longitudinal growth performance was compared in the two groups by multiple linear regression analysis using successive attained anthropometric measurements as dependent variables with previous measurements and diet type as independent factors on a within subject basis, using a quadratic fit.

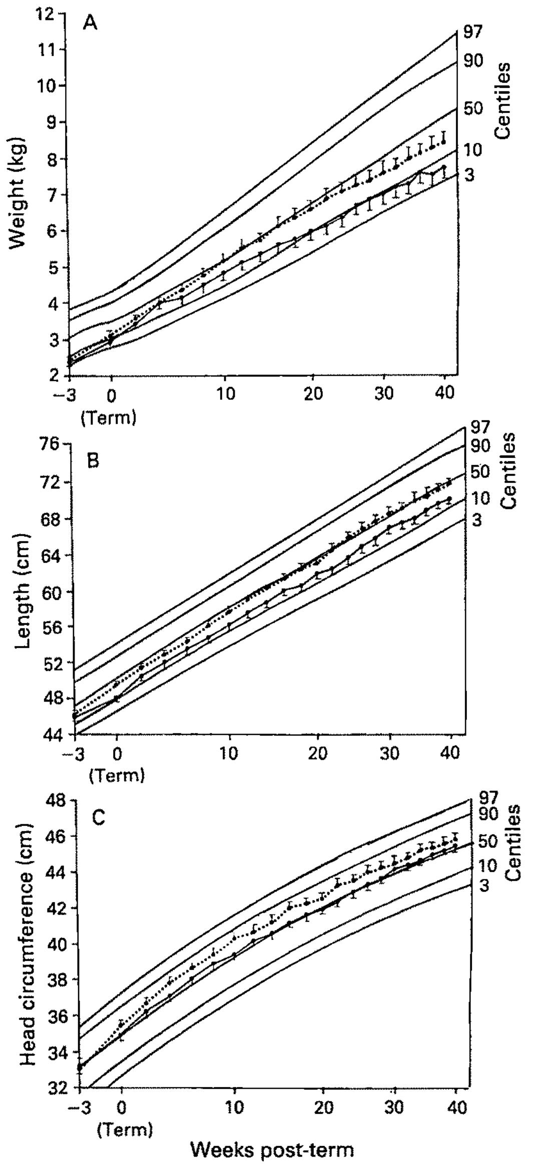
Based on previous follow up data on preterm infants,[5] sample size was calculated to detect a 10% difference in weight gain to 9 months postterm at 5% significance and 80% power.

Results

The two groups of infants were closely matched in terms of their birth weight, gestation, and sex ratio. Postmenstrual age and weight at point of entry to the study—that is, when the transfer to the post-discharge diet was made—were also very similar for each group (see table 2). One infant randomly assigned to the standard formula became unwell before discharge and required surgery at another hospital. This baby could not be studied in the postnatal period, leaving 15 subjects in this group.

GROWTH

The growth performance of the two diet groups is shown for both sexes plotted on combined centiles in the figure (based on Gardner-Pearson growth charts). Differences between the diet groups are apparent on visual inspection of the charts. At 37 weeks' postmenstrual age, on



Longitudinal data (means (SE)) for (A) body weight, (B) body length, and (C) head circumference in babies fed a standard formula (solid line) versus those fed the follow-on formula (dotted line) from recruitment (mean three weeks' preterm) to 40 weeks post-term. Data are for both sexes combined; centiles derived from Gardner-Pearson charts (published by Castlemead, UK).

entry to the study, body weight lay between the 3rd and 10th centiles. By 9 months this was still the case for infants fed on standard formula, but those fed the nutrient enriched formula lay close to the 25th centile. Body length at 37 weeks' postmenstrual age lay close to the 25th centile in both groups. This was still so at 9 months for the infants fed the standard formula but those fed the enriched formula remained close to the 50th centile from 4 months post-term onwards. Significant differences between feed groups in body weight and length were seen at some individual time periods. However, a within subject analysis to examine longitudinal growth rate, using a quadratic fit, showed significant increases in weight gain ($p<0\cdot005$) and linear growth ($p<0\cdot01$) in the group on a nutrient enriched diet compared with those on the standard formula throughout the whole 9 month study period. While head growth data indicate a divergence between diet groups, most noticeable in the 2–6 month period, the difference in head growth rate between groups did not reach significance. Skinfold thicknesses (triceps, subscapular) did not differ significantly between the diet groups.

FEED INTAKE AND WEANING

During the periods 0–3 months and >3–6 months post-term, formula intake was the same in the two groups (see table 3). The trend towards reduced formula intake in the group fed the nutrient enriched milk at >6–9 months was not significant. In addition, there was no significant difference in the time of introduction of weaning foods: mean (SD) corrected age 10·7 (4·5) weeks in the standard formula group and 12·6 (4·2) weeks in the follow-on preterm formula group.

FEED TOLERANCE

We collected data on the number of vomits, possets, and bowel motions for each infant on a day to day basis, and also the number of episodes of colic, the stool consistency and its volume (using charts developed for studies of gastrointestinal upset in UK and Gambian children by the MRC Dunn Nutrition Unit).[8]

There was no difference between the diet groups for any of these factors, although individual variation was large (see tables 4 and 5), and there was an overall trend towards larger stool weights in infants receiving the follow-on formula.

Table 4 Feed tolerance. Data are median (interquartile range)

	Vomits/day	*Possets/day*	*Colic episodes/2 weeks*
Standard term formula (n=15)	0·9 (0·1–1·8)	1·7 (1·1–4·2)	1 (0–3)
Follow-on formula (n=16)	0·6 (0·2–1·3)	2·3 (1·0–5·5)	1 (0–4)

Table 5 Stool data at corrected postnatal ages. Data are mean (SE)

	0–3 Months	*>3–6 Months*	*>6–9 Months*
Standard term formula (n=15)			
No/day	2·0 (0·18)	1·5 (0·06)	1·8 (0·08)
Size*	3·1 (0·15)	3·4 (0·07)	3·3 (0·08)
Consistency†	2·9 (0·11)	2·5 (0·14)	2·4 (0·07)
Follow-on formula (n=16)			
No/day	2·2 (0·24)	1·9 (0·14)	2·0 (0·31)
Size*	3·3 (0·14)	3·4 (0·15)	3·6 (0·17)
Consistency†	2·8 (0·13)	2·3 (0·16)	2·5 (0·09)

*Size graded (approximately) by mother using comparison charts: 1=1 g, 2=2·5 g, 3=5 g, 4=10 g, 5=20 g.

†Consistency graded by mother using comparison charts: 1=hard, 2=formed soft, 3=mushy soft, 4=runny, 5=watery.

Discussion

In this study infants whose mothers chose to bottle feed were randomly assigned to a special nutrient enriched follow-on preterm formula or to a standard term formula, to be used either alone or in conjunction with weaning foods throughout the first 9 months post-term. During this study period the infants fed on the special formula gained a higher centile for weight, length and head circumference; and for weight and length gain velocities, the advantage for the special formula was significant.

The special follow-on preterm formula was designed to be intermediate in its composition between a standard term formula and a special preterm formula, though in fact its composition falls within the current Department of Health and Social Security, European Society for Gastroenterology and Nutrition, and European Community guidelines for a standard formula.[9, 10] An increased energy content of 72 kcal (302 kJ)/100 ml (an increase on the 68 kcal (286 kJ)/100 ml in most standard formulas) was incorporated to promote utilisation of the increased protein intake, while recognising that excessive energy intake might result in unnecessary fat gain. The protein content was set at 1·85 g/100 ml, around 20% higher than in a routine highly adapted formula, in order to promote catch-up growth.

Metabolic bone disease is very common in preterm infants[11, 12] and many leave hospital with underminerahsed bones.[13] The follow-on formula provided a substantially higher calcium and phosphorus content than that found in most standard formulas. Relatively high levels of trace minerals (zinc and copper) were incorporated to attempt to replete the low body stores expected after preterm birth, compounded by the negative balance status observed in this population during the early weeks,[14, 15] and specifically to address the concern, expressed by others, that low zinc status in the period after discharge could result in suboptimal growth.[16] Levels of a number of vitamins have been increased proportional to the projected increased growth rate.

The higher growth rate observed in the infants fed the special formula was likely to have related to the generally higher nutrient intake, though the high calcium and phosphorus intake could have been especially important for the increase in linear growth. We and others have shown that deficient bone mineral intake in infants born preterm is associated with reduced linear growth in the neonatal period[17, 18] and with reduced attained length at 18 months.[7] This aspect of the study will be explored further when we report the results of the sequential bone mineral content measurements made concomitantly. The increases in weight and length (together with a trend towards increased head

Table 6 Skinfold thickness and diet after discharge at corrected postnatal ages. Data are mean (SE) in mm

	0–3 Months	*>3–6 Months*	*>6–9 Months*
Standard term formula			
Triceps	7·7 (0·3)	8·9 (0·6)	8·7 (0·7)
Subscapular	7·4 (0·6)	7·2 (0·6)	6·9 (0·7)
Follow-on formula			
Triceps	7·9 (0·4)	8·6 (0·4)	9·2 (0·4)
Subscapular	6·8 (0·3)	6·8 (0·4)	6·7 (0·4)

growth) without a corresponding increase in skinfold thickness (table 6) indicates that the improved growth in infants fed the nutrient enriched formula cannot be attributed simply to increased body fatness.

The most important question raised by our data is whether the improved growth after discharge of infants fed on the special formula will be related to improved developmental status and body size at subsequent follow up. We are conducting formal follow up examinations on this cohort with detailed neurodevelopmental testing at 9 and 18 months post-term and the findings will be reported. Our previous studies have indicated that the early weeks may be critical for the nutrition of the preterm baby and that a relatively brief period of dietary manipulation may have a profound influence on developmental scores 18 months later.[5] The possibility that this 'sensitive' period extends further into infancy, beyond the period of hospitalisation, is a hypothesis that will be tested on this cohort. The investigation we report is a relatively small initial study and targeted to detect differences between groups in short term growth. Only large differences in developmental quotients (albeit of the magnitude observed in our previous nutritional studies) could be detected here. Nevertheless, even if longer term effects could not be shown in this study, the improved growth rate throughout infancy in the babies fed the special formula must be regarded as a potential clinical advantage in terms of improving their general nutritional status.

It was interesting that the special formula group had the same volume of intake as the infants fed the normal formula during the first 6 months. Some previous investigators[19 20] have suggested that babies regulate their milk intake in relation to the energy or nutrient density. Yet we found no down regulation of volume of intake in the special formula group, so that these babies achieved increased nutrient intake. Our data add to the broader debate on the issue of appetite regulation in the infant.

Premature babies in this study achieved their better growth performance after discharge without an increase in gastrointestinal disturbance or other observed problems. These data support the concept of using specially designed formulas throughout the first 9 months postterm for bottle fed babies born preterm. Our data do not address breast feeding in this group; this is an area for further investigation.

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Varicella zoster virus DNA in throat swabs of vaccinees

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Abstract

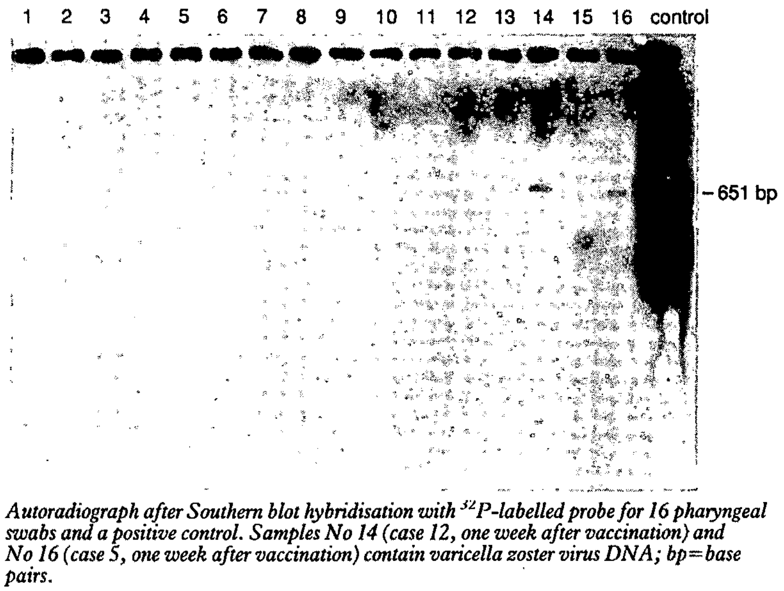
Ninety throat swabs from 30 healthy children who received varicella vaccine were tested for varicella zoster virus DNA by the polymerase chain reaction. Seroconversion was observed in 27 of 30 (90%) vaccinees. The positive rates were 7·4% (2/27) at one week and 0% (0/27) at four weeks after vaccination. These rates were considerably lower than those in normal children with varicella.

Varicella, caused by primary infection with varicella zoster virus, is a common and highly contagious disease of childhood. The study of the pathogenesis of varicella zoster virus infection had been limited by technical problems with the laboratory detection of it. We established a polymerase chain reaction method for detecting varicella zoster virus recently,[1] and we have used it to examine throat swabs of normal children with varicella. We could detect the viral DNA in 26·2% (11/42) of the children during the incubation period and in 89·7% (35/39) after clinical onset of the disease.[2]

Live attenuated varicella vaccine, developed in Japan in the early 1970s, has been widely used in normal children in Japan since being licensed in 1987. We describe here the results of our attempts to detect viral DNA in the pharynx of normal varicella vaccine recipients by the polymerase chain reaction technique.

Methods

This study was conducted at the paediatric outpatient clinic of Showa Hospital over a three month period in 1990. Thirty healthy children of both sexes who had no history of varicella, 1 to 9 years of age, received live attenuated varicella vaccine (lot 016 and 017, Oka strain, Biken). Two sera (before and four weeks after vaccination) and three throat swabs (before one week and four weeks after vaccination) were obtained from each of them. One throat swab was also obtained from each of 15 healthy children who were used as negative controls; their ages ranged from 2 to 14 years. All swabs were placed in 3 ml of phosphate buffered saline and stored at −80°C before analysis. After the project was explained parental consent was obtained.



Autoradiograph after Southern blot hybridisation with ^{32}P-labelled probe for 16 pharyngeal swabs and a positive control. Samples No 14 (case 12, one week after vaccination) and No 16 (case 5, one week after vaccination) contain varicella zoster virus DNA; bp=base pairs.

The serum samples were examined for humoral immunity to varicella zoster virus by the two assays previously described; the immune adherence haemagglutination assay[3] and the indirect fluorescent antimembrane antibody assay.[4]

The throat swabs were tested for varicella zoster virus DNA by the polymerase chain reaction; this has been described previously.[2] Briefly, DNA samples extracted from the throat swabs were first heated at 94°C for 10 minutes to denature the DNA and then subjected to 30 amplification cycles. Annealing was performed at 60°C for 2 minutes, extension at 72°C for 5 minutes, and denaturation at 90°C for 1 minute. The pair of primers used in this study were a region of glycoprotein I, and the length of amplified product was 651 base pairs. The preliminary testing made sure that the primers amplified Oka varicella zoster virus from lots 016 and 017. The amplification reaction was carried out in a DNA thermal cycler (Perkin-Elmer/Cetus). Direct gel electrophoresis with ethidium bromide staining and Southern blot hybridisation with a homologous ^{32}P-labelled cloned DNA probe (figure) were applied for detection of the amplified product. In this system varicella zoster virus DNA could be detected at a level of 5×10^3 copies by ethidium bromide staining, and 50 copies by Southern blot hybridisation. Varicella zoster virus DNA extracted from cells infected with the Oka strain was detected by direct gel electrophoresis and by Southern blot hybridisation and was used as a positive control in every experiment.

Results

The table shows the age and sex of the 30 vaccinees, vaccine lot number, and the results of serological and polymerase chain reaction studies. Clinical observations were made daily

The results of serological and polymerase chain reaction studies in the vaccinees. Day 0 is the day of vaccination

Case No	Age/sex	Vaccine lot	Antibodies (IAHA/FAMA)		PCR analysis		
			Day 0	Day 28	Day 0	Day 7	Day 28
1	1/F	016	<2/<4	8/16	–	–	–
2	3/F	016	<2/<4	8/32	–	–	–
3	2/M	016	<2/<4	16/16	–	–	–
4	2/M	016	<2/<4	8/16	–	–	–
5	4/F	016	<2/<4	8/8	–	+	–
6	1/F	016	<2/<4	8/4	–	–	–
7	1/F	016	<2/<4	16/16	–	–	–
8	2/M	016	<2/<4	8/8	–	–	–
9	4/F	016	<2/<4	64/64	–	–	–
10	2/M	016	<2/<4	16/4	–	–	–
11	1/F	016	<2/<4	8/8	+	–	–
12	2/F	016	<2/<4	4/4	–	+	–
13	5/M	016	<2/<4	<2/<4	–	–	–
14	2/F	016	<2/<4	16/16	–	–	–
15	1/M	016	<2/<4	16/8	–	–	–
16	2/M	016	<2/<4	8/8	–	–	–
17	9/M	016	4/<4	64/32	–	–	–
18	1/M	016	<2/<4	8/8	–	–	–
19	3/M	016	<2/<4	16/8	–	–	–
20	8/F	016	<2/<4	8/8	–	–	–
21	6/F	016	<2/<4	4/4	–	–	–
22	4/M	016	8/4	128/64	–	–	–
23	1/F	017	<2/<4	16/8	–	–	–
24	5/M	017	<2/<4	32/32	–	–	–
25	1/M	017	<2/<4	4/4	–	–	–
26	5/F	017	<2/<4	32/32	–	–	–
27	4/M	017	<2/<4	32/32	–	–	–
28	7/F	017	<2/<4	8/8	–	–	–
29	1/F	017	<2/<4	16/8	–	–	–
30	3/M	017	<2/<4	8/4	–	–	–

Not detected (–) and detected (+) by Southern blot hybridisation. IAHA=immune adherence haemagglutination, FAMA=fluorescent antimembrane antibody; PCR=polymerase chain reaction.

by their mothers for four weeks after vaccination, and no systemic reactions were recorded. In 27 of 30 (90%) vaccinees, seroconversion was observed by both the serological assays. The viral DNA could be detected in three of 90 (3·3%) throat swabs by the polymerase chain reaction with Southern blot hybridisation. No viral DNA could be detected by the method with direct gel electrophoresis. One positive swab was found before vaccination and two swabs were positive one week after vaccination. The three vaccine recipients whose swabs contained varicella zoster virus DNA showed seroconversion by the both serological assays. In the swabs of negative controls no viral DNA was amplified specifically.

Discussion

Isolation of varicella zoster virus from the pharyngeal area is usually difficult in normal children with varicella. One explanation for this is that cell culture technique is not sensitive enough to detect the virus. Recently we established a polymerase chain reaction method for detecting varicella zoster virus DNA and this has been proved to be much more sensitive than viral culture with the previous studies.[1,2] The viral DNA was amplified in 100% (20/20) of vesicle samples and in 83·3% (5/6) of crusts from normal children with varicella.[1] Identification of the viral DNA from throat swabs in 26·2% (11/42) during the incubation period and in 89·7% (35/39) after clinical onset[2] indicates that the pharynx is a site for replication of the virus in normal children with varicella.

A live varicella vaccine has been extensively used in Japan, and its safety and effectiveness have been recognised for immunocompromised and immunocompetent children. The magnitude of viral replication of the vaccine virus is less than that of the wild type virus, and it has been considered to be unlikely that the vaccine virus spreads widely to susceptible children. In two institutions in Japan no infection was observed to be transmitted clinically or serologically from normal and handicapped vaccine recipients without a rash to susceptible children.[5,6] Our investigation of varicella zoster virus DNA in throat swabs by the polymerase chain reaction demonstrated that positivity rate and quantity of detected viral DNA in normal vaccine recipients were considerably lower than those in normal children with varicella. These results may suggest that the Oka strain and the wild type strain of varicella zoster virus have different sites of replication in healthy children. If transmission of the virus occurred mainly by airborne route from the pharynx, our data might explain the low transmissibility of the virus from vaccine recipients.

Although the varicella zoster virus DNA was detected in the swab of a vaccinee before vaccination (case 11), we believe it was not contamination and non-specificity. The viral DNA was not amplified in negative controls, and the primers used were certified as having no homology with five other human herpesviruses (herpes simplex virus types 1 and 2, human herpesvirus-6, human cytomegalovirus, and Epstein-Barr virus).[1] We presume that the swab was taken just after unknown exposure to a wild strain and varicella was prevented by immediate inoculation of vaccine.

The polymerase chain reaction is very sensitive and is useful to investigate the pathology of varicella zoster virus infection. To justify our speculations, further studies using the method should be carried out with more samples taken. Studies should also be attempted on blood specimens obtained from immunocompromised and immunocompetent vaccinees.

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Advantages of working in the developing world during paediatric training

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Background

After three years as a paediatric senior house officer in the north of England, I volunteered to work for nine months in Wau, southern Sudan, with Médecins Sans Frontières as part of the international relief effort. The experience and knowledge gained, both medical and in personal terms, are described in this article in the hope of encouraging more doctors to take time out to work in developing countries.

Southern Sudan has been intermittently in open rebellion against the north since gaining independence from Britain in the 1950s. The black and mainly Christian or Animist southerners have been unhappy with political and religious domination from the Islamic north, especially attempts to impose Sharia (Islamic law) since 1983. The Sudanese People's Liberation Army (SPLA) now controls most of the rural areas of southern Sudan except for some of the larger towns where the northern army maintains large garrisons.

During the 1988 disruption of agricultural production and supply by the fighting created a large refugee population with malnutrition and starvation on a huge scale. At least 250 000 people starved to death. By 1989 the International Committee of the Red Cross (ICRC) was finally given authorisation to airlift food and medical supplies to the main southern towns of Wau, Juba and Malakal, all effectively under siege by the SPLA.

The 150 000 or so people of Wau were sad, tired, and hungry having suffered starvation, large scale intertribal violence, and massacres by the army. In the refugee camps huddled and unsanitary conditions led to high incidence of diarrhoea and other infections, frequently leading to death.

What did I do?

I was a member of a four person team from Médicins San Frontières. There was one other doctor who was to work in and try to rejuvenate two primary health care clinics and run a small HIV prevalence survey. There was also a nurse whose role was in training and motivation of staff in the hospital and the implementation of the vaccination and therapeutic feeding programmes. Finally there was a builder to carry out various renovation works to the hospital and health centres and to supervise the vaccine cold chain. As a paediatrician in the government hospital my aim was to improve services in the children's ward and morale in the rest of the hospital. As the main hospital for the region the Wau hospital was designed for up to 500 patients and 30 doctors. When I arrived there were little more than 100 occupied beds supervised by five local doctors who had mostly lost interest as a result of the general decline in morale that had taken place. Most of the medical work was done by minimally trained medical assistants who had few facilities, equipment, or drugs. Corruption was rife with most government supplied drugs soon finding their way to the marketplace. With the knowledge gleaned from previous involvement of Médicins Sans Frontières, the staff of the paediatric ward had already developed a degree of organisation that helped them to contribute significantly to the control of a seasonal epidemic of meningococcal meningitis that was rife when I arrived. In the hospital alone we treated 150 cases with a 10% mortality while hundreds more were occurring in and around town with much higher losses. This was also a good time to reactivate the vaccination programme in Wau for which a structure and staff still existed but, inevitably, refrigerators and generators did not work and all the vaccines were spoiled. With technical support and supplies from Médicins Sans Frontières and UNICEF the vaccination programme was recommenced with a vaccine campaign for meningococcus serogroups A and C for 50 000 people. Subsequently with further support and encouragement the programme of childhood and antenatal vaccinations was successfully recommenced.

I had intended to spend as much of my time as possible on the paediatric ward in teaching, training, and generally organising. Inevitably, however, a lot of time was taken up with management of individual cases. Initially malnutrition was the biggest problem. We built a grass roofed kitchen area before the onset of the wet season and from here we fed about 120 children daily with milk powder/wheatflour porridge and bean stew. Children were entered into the feeding programme on the basis of being less than 80% optimal weight for height. The worst cases were admitted to the ward for further supplementation with high energy milk (milk powder/sugar/oil) with the weaker ones sometimes being fed via nasogastric tube. A similar number of childern were also fed with weekly rations. Monthly rations were being delivered to tens of thousands of people by the ICRC who, additionally, organised daily feeding for several hundred children in the refugee camps. By midsummer, with a reasonable local harvest and some overland food movement allowed by a temporary ceasefire to supplement the air lifted supplies, the nutritional situation had improved considerably.

The simple childhood infections also caused much morbidity and mortality. The three local medical assistants were seeing up to 100 outpatients daily and we had up to 30 inpatients. Common causes for admission were severe diarrhoea, malaria, and pneumonia. Various wasting illnesses were common in addition to starvation: tuberculosis, kala-azar, and almost certainly HIV infection, the prevalence of which was between 2% and 10% in various populations surveyed. Neonatal tetanus was a frequent and difficult problem; burns and trauma were common as were leprosy and onchocerciasis. By the end of my stay the ability of the nurses, medical assistants, and myself to recognise and treat most of the common problems was improving.

Our drug supply was flown in from Khartoum, mostly in the form of standard emergency kits supplied by UNICEF. On the ward we could use intravenous drips and nasogastric feeding as well as facilities to perform minor operations (usually draining abscesses) under intravenous anaesthesia with ketamine. I was also able to provide some medical input to two clinics run by Catholic nuns. My colleague from Médicins Sans Frontières was supporting two other such clinics and the ICRC had two or three nurses running dispensaries in the various refugee camps.

After the military coup in Khartoum in June 1989 the situation became more difficult; fighting recommenced and the government became less cooperative with the relief effort to the extent of withdrawing authorisation for the ICRC airlift in October. The project continued but without supplies from Khartoum could not remain effective. I left in December and the two last team members were withdrawn in February 1990. The situation since then has deteriorated further. Despite the need being even greater, with seemingly less government cooperation and world attention focused elsewhere, the ability of the various aid agencies to help has declined.

What did I learn?

Most obviously, although not necessarily most importantly, I gained experience by seeing and treating a vast array of diseases that I would be unlikely to see in the UK. I learned about many new illnesses from personal experience and from teaching by local people. I learned by having to manage and 'make do' with meagre resources using simple, locally available technology. For example, how to use BCG vaccine as a diagnostic tool when tuberculin purified protein derivative is unavailable or how to optimise the formulation of a high energy milk for both children with marasmus and kwashiokor with their different needs. I learned to work in a team at various levels, within the whole town with the local authorities and other aid workers, within the hospital with the local doctors, and on the ward itself. Here staff motivation was crucial and differences of opinion, no matter how seemingly trivial, particularly between members of different tribes could become so heated. Probably the most important lesson came from having to be constantly aware of the health needs of an entire community. In the UK one's working objectives are usually fairly clearly defined especially when involved in day to day patient care. In Africa it was most important to think in terms of one's influence on the entire health care system rather than just the individual patient; thinking about nutrition, vaccination, sanitation, and education which are all too easily forgotten in the UK. One had always to be aware of the consequences of each everyday action and in particular to be careful not to introduce any practice or technology that the local people would not be able to sustain.

Not only did I learn from a professional point of view but also from a personal one. Witnessing the kind of suffering that was taking place was not pleasant but seeing how well, stoically, and even happily that so many people coped with their lot was an enriching experience.

What did I contribute?

This is a difficult question to answer. Curative work was satisfying for me but without doubt the most useful contribution that the well trained expatriate can make is in the field of training, passing on the skills that he has been fortunate enough to learn. Such a role would be better filled by members of the local community who had been appropriately trained, but in developing countries suitably (and thus expensively) trained locals are likely to remain in short supply for the foreseeable future leaving a need for expatriate workers.

What are the problems of going?

It can certainly be unsettling. Several months had passed before I felt settled at home and at work. I had also to fill in with several months of locum work before I could find a suitable career registrar post. I wonder whether job interview panels consider such experience interesting but perhaps not quite as serious as a period at home or abroad in a research institution. For me, although obviously not for everyone, developing world experience was equally serious but more rewarding.

What preparation is needed?

There are many organisations through which one can find work in the developing world, many of which have trouble recruiting motivated volunteers. The Bureau for Overseas Medical Service Newsletter is a good place to start looking. The more experience gained before going abroad the better, but this has to be balanced against the greater difficulty of taking time out from higher up the career ladder. Junior registrar level is probably a good time to go, ideally having done one of the three month diploma courses in tropical medicine and hygiene at the London or Liverpool schools.

I have no doubt that the huge problems faced by the developing world can only be resolved by international political and economic reform and not by individual effort no matter how well meant. However, by working in the developing world we can improve our own understanding of, and more readily empathise with, the problems of others, perhaps help a little to resolve some of their suffering and in the process learn a great deal that will be of personal and professional value in years to come. I would urge any doctor who feels motivated towards working in the developing world to take the plunge. The benefits are enormous.

Commentary

Dr Williams' experience of a period in the Sudan will bring back memories to many others who have had the privilege of helping for a period in the developing world. I was, however, sorry he did not have the opportunity to visit the resource centre set up specifically to help such individuals at the Centre for International Child Health in the Institute of Child Health.

Since Professor Andrew Tomkins has taken over the responsibility of the unit, the material in the resource centre has been extended and is being updated. Paediatricians going overseas will always be welcome.

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Measuring compliance with inhaled medication in asthma

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Abstract
Using an electronic inhaler timer device (Nebulizer Chronolog), compliance with the prescribed frequency of inhaled prophylactic medication in 14 asthmatic children was measured. Underuse occurred in 55% of study days while overuse occurred in only 2%. Such devices provide an important new tool for investigating inhaled drug compliance.

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Asthma continues to be a major and rising cause of morbidity in childhood,[1] despite advances in drug treatment and escalating presciption of antiasthma medication.[2] Poor response to treatment may occur for many reasons but one increasingly recognised problem is failure to adhere to the prescribed treatment. This may be especially important in asthma where good symptom control often depends on the patient taking regular preventative medication.

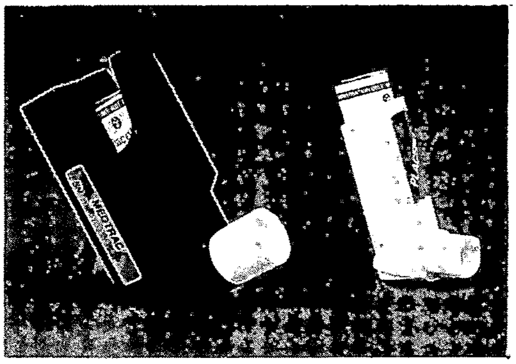
Previous studies in asthmatic subjects have pointed to poor compliance with treatment. However, the methods described have either been indirect, such as prescription uptake, or have averaged the effects of drug taking over time as with monitoring drug concentrations.

More recently, inhaler timer devices have been developed. One example, the Nebulizer Chronolog (Forefront Technologies Inc, Lakewood, Colorado), electronically counts and times each actuation of a metered dose inhaler (MDI). This device replaces the normal plastic inhaler holder (figure) and can be used with all types of aerosol canisters allowing direct monitoring of inhaler use.

Methods

We used the Nebulizer Chronolog in a pilot study investigating compliance with inhaled prophylactic treatment in children (n=14; age 9–16 years; M:F 6:8). All had moderate to severe asthma, were using MDIs, were being treated with prophylactic inhaled corticosteroids, and were judged to have satisfactory inhaler technique. Verbal consent for the study was obtained from the children and their parents. All were aware that the device would 'count' the number of actuations but, in general, were not aware of the precision of the recording. The subjects were issued with an initialised Nebulizer Chronolog and a diary card with instructions to score their daily symptoms and note their inhaler use.

After one to three months the Nebulizer Chronolog and diary cards were returned. The information stored in the device was read and analysed by dedicated computer software and a report, detailing medication use, prepared. For each individual patient day, the prescribed use, recorded use (Nebulizer Chronolog), and reported use (diary card) of prophylactic medication were compared. A 'compliant day' was defined as one in which the prescribed number of puffs were taken at appropriate times.



A Nebulizer Chronolog compared with a standard metered dose inhaler.

Compliance of children with prophylactic inhaled medication

Prescribed frequency (times/day)	*No of children*	*No of study days*	*Reported compliance in days (%)**	*No (%) of days of recorded complicance*	*No (%) of days of recorded underuse*	*No (%) of days of recorded overuse*
2	5	233	96	166 (71)	63 (27)	5 (2)
3	3	80	90	27 (34)	49 (61)	4 (5)
4	6	224	69	41 (18)	181 (81)	2 (1)

*Expressed as a percentage of completed diary card days.

Results

Most subjects had no difficulty with the device as an inhaler holder. Indeed, two expressed a preference for the bulkier Nebulizer Chronolog. Satisfactory data were obtained in all 14 subjects from the Nebulizer Chronolog while diary card reporting was unsatisfactory in four.

Underuse was always found to be the omission of a time of administration rather than not taking enough puffs, whereas overuse consisted of taking more than the prescribed number of puffs. Overall, despite evidence of active asthma, underuse of prophylactic medication was recorded by the Nebulizer Chronolog on 55% of the study days (table). Perhaps surprisingly, overuse was only recorded in 2% of study days. Seven patients failed to take any prophylactic medication on at least one of the study days.

We found appreciable discrepancies between reported and recorded MDI use (table) with all children reporting better compliance than recorded, despite knowing that the device would 'count' the number of actuations. Also, although the numbers were small, we were interested to note differences in compliance with different frequencies of administration, with the five patients on a two times a day regimen being compliant on 71% of days compared with only 18% for those on a four times a day regimen.

Discussion

This pilot study demonstrates the feasibility of accurately monitoring long term inhaler use with an inhaler timer device.

One potential confounding factor with such devices is actuation without inhalation, as in the practice of 'test firing'. Only one subject, who had long periods of omitting to use his inhaler was noted to have numerous actuations (77 in 13 minutes) immediately before a clinic attendance. In practice, we considered that by actuating the device at an appropriate time the patient was probably inhaling it.

It has been reported that including children in prospective asthma trials may improve compliance rates, either because of a placebo effect or because of more consistent management.[3] Despite this, the compliance rates we recorded were variable and often poor. The discrepancies noted between reported and recorded use highlighted again how poor diary cards are at capturing an accurate record of medication use.[4]

We were particularly interested in the changes in compliance with prescription frequency. Inspection of the printouts showed that, in those on a four times daily regimen, underuse usually resulted from missing out the middle doses. Only occasionally was medication not taken at all on any regular basis. The superiority of twice daily regimens was striking.

We conclude that an inhaler timer device provides a useful method for investigating compliance with inhaled medication in children. One important application of such devices may be in controlled drug trials where patients with poor compliance could easily be separated from those with poor treatment response.

We gratefully acknowledge support from the Medical Research Fund Grant of the University of Glasgow. Dr Coutts was funded by the Cystic Fibrosis Research Trust.

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CONTEMPORARY HISTORY

A girl in my arms: a story of a paediatrician from Vukovar

Branka Šipek

I finished medical school in Zagreb and have worked as a paediatrician in Vukovar for 17 years. I worked in the Vukovar hospital until it fell into the hands of the Yugoslav Federal Army. This is the story of my last patient.

The story

In the afternoon of 15 November, 1991 a heavy artillery grenade fell on the civilian shelter in the basement of the destroyed Eltz castle. The shelter was actually a wine cellar, with barrels full of wine, and 30 civilians lived there for months. The grenade killed nine of them instantaneously. The family of one of our nurses was killed on the spot, including the nurse herself, her 3·5 year old son, and her mother-in-law. Her husband was wounded in the same shelter and died in hospital. One woman in the fourth month of pregnancy was wounded, and was hospitalised with a serious pneumothorax. Her husband was killed on the spot. In one family, three members were wounded: two girls, aged 6·5 months and 5 years, and their mother. Her brother and mother-in-law were killed. The father was outside at that moment. Later, when he came to visit his wife and children in the hospital he told us of the horrible deaths in the shelter: the cellar was flooded, and detached arms and legs and corpses were floating in blood and wine.

The 6·5 month old girl had a wound of the left thigh, measuring 14×7 cm, and another in the gluteal region. The shrapnel penetrated the abdominal cavity, with consequent paralytic ileus and septic shock. The child was operated on immediately and was in a critical condition. The operation was performed by Drs Njavro and Vidović in the cold operating theatre (part of the antiatom bomb shelter). We disconnected the only incubator left and used its heating plate to keep the baby warm. Our anaesthetist, Dr Kušt, brought in a hair drier and used it to warm the air in the room. The baby received several blood transfusions. We did not have any frozen blood and had to use our own. Also, we could not follow the proper treatment regimen because we had no antibiotics appropriate for her age and had to give what we had for other patients. Even worse, we did not have sterile water, saline, glucose, or any other solution to dilute the antibiotics. We used what we had left from the large donation from Germany that came in the summer. It was a solution for infusions, inappropriate for the girl's age. She had a nasogastric tube and urinary catheter and a constant intravenous infusion. She vomited most of the time. She lay in a cot next to her mother and sister, who shared the same bed. The baby was practically dying in front of her mother's eyes. I would sit by her and hold her head in one position, so that the infusion needles would not fall out from the veins in the neck, the only ones we could inject, while her mother and sister caressed her and held her hands. Later we managed to move her cot some 2 m from them, so that they did not constantly watch her suffering. Her father held her leg when we changed the bandages. We tried to persuade him not to do that, because her thigh was a large open wound, but he refused and held her in his arms. After two days, the surgeons had to perform a necrectomy of the wound, which even enlarged the wound opening, so that the bone was visible.

The night of the second operation was the night when the Yugoslav Federal Army entered the hospital. On the next morning the transportation of the patients and personnel was organised. I knew it would take a long time so I took the girl and asked the driver of an international Red Cross ambulance if I could sit in his car for a while. It was bitterly cold outside. I sat there with the girl in my arms. This was her first postoperative day and her condition was getting worse. After two hours of waiting I was taken to a Red Cross ambulance from Belgrade. One nurse and a female doctor from Belgrade were with us. The convoy took the route through Negoslavci, an undamaged village, populated mostly with Serbs. We stopped there and waited on the road for two hours. The doctor from Belgrade was correct but cold and reserved, telling us from time to time that the Croatian government did not want us and that they did not know what to do with us. The drive over large holes and bumps on the roads was almost unbearable; the infusion needles fell out and I had to put them back, while the life in that small body just barely flickered in my hands. A woman in the ambulance, who had given birth to the last infant in Vukovar two days before, started bleeding. My little patient's neighbour from the shelter in Eltz castle, in her fourth month of pregnancy and with a pneumothorax, was in a critical condition and died during the trip. I could not tell where we were heading. During the trip I asked several times to be taken immediately to a hospital with the child because she would not survive the next few hours. The doctor from Belgrade finally agreed to leave the convoy and

Vukovar Medical Centre, Vukovar, Croatia
Dr Šipek is now a refugee in Zagreb.

we left for the Medical Centre in Sremska Mitrovica and went to the surgery ward. The paediatric surgeon who examined the child confirmed my suggestion of immediate transport to the Children's Clinic in Belgrade. A federal army officer agreed to organise the transport to Belgrade. The girl's family stayed in Sremska Mitrovica and said that they would wait for their daughter. They had nowhere to go and nothing to leave—everything they had was destroyed. If their daughter was to die, they said, they had to know where she was buried.

I do not know what happened to her. I cannot call my colleagues in Belgrade to inquire about her condition. I cannot contact her parents. I hope we eased her pain and took some of her suffering from her little shoulders. I carry the pain and suffering from her eyes in my dreams.

I thank Dr Ana Marušić who took the interview and kindly did the translation.

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TYPES OF PSYCHIATRIC TREATMENT

Individual psychotherapy

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This is the second of a series of articles on treatment of child psychiatric disorders.

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Definition

Individual psychodynamic psychotherapy involves one to one treatment using verbal and play techniques. The treatment is based on working with the patient in the here and now—that is, on the relationship that develops between the patient and the therapist. Links are constantly made from this to past experiences and current external relationships. The patient is understood in terms of developmental pathways, unconscious process, defence mechanisms, and attachments.[1–4]

Which patients will benefit?

Individual psychotherapy can be used with children from about 18 months to 2 years of age and across the age range up to 21 years. Parent-child psychotherapy is used before 18 months with the therapist working with the parent and the child or with the child with the help of the parent.

One of the features of individual treatment is to try and provide a consistent regular reliable setting for the treatment. This means wherever possible making the treatment sessions on the same day at the same time in the same room and with the same play equipment and toys available. This may be in a child and family mental health clinic or in a department of child psychiatry or department of psychological medicine. Children can also be seen at school if a room can be made available, whether primary, secondary, or a special school. Children and young people can also be seen in hospital on a paediatric ward, a child psychiatry ward, an adolescent unit, or a day unit. The child or young person does need some privacy and if at all possible some physical space without too many intrusions such as telephone calls or people in and out.

Play materials provided vary with age and preschool children generally have crayons, paper, plasticine, plastic small farm and wild animals, simple plastic figures, cars, and pipe cleaner dolls. Primary schoolchildren are more inclined to use paper, scissors, glue, felt tip pens, cars, a ball, and string as well as plasticine, the animals, and figures. Secondary schoolchildren may prefer to talk, although many of them like to draw or write.

Which children and young people can benefit?

Children and young people can become distressed, confused, and depressed by life's adversities. Some of them may have particularly difficult circumstances and some may be vulnerable children. If a child or young person becomes stuck and unable to resolve the difficulties with the help of the usual resources—parents, teachers, family friends, their general practitioner, or a counsellor in school—they may benefit from treatment. Other children and young people may be much more floridly troubled with very worrying or disturbed behaviour dangerous to themselves or others. Very disturbed children with psychotic features can respond well to treatment, children with developmental delay can also improve considerably. I would like to suggest nine categories of problems where individual psychotherapy should be considered.[5]

(1) Family breakdown and reconstituted families. Some children may be caught between warring parents or in a very difficult new family situation. Individual treatment perhaps with family therapy can help the child sort out their own feelings and reactions to the emotional turmoil.[6]

(2) Life events such as bereavement loss of a parent or a sibling, physical or mental handicap in a sibling, or suicide of a parent or sibling can leave many children and young people confused and bewildered and they can benefit from individual treatment.[7 8]

(3) A child or young person with chronic physical or mental handicap may have serious emotional difficulties and conflicts that can prevent them from being able to use what mental or physical capacities they do have. Individual treatment can liberate them to enable them to develop in ways that they can and to enable them to find some satisfaction in the relationships they can develop. Adolescents may need particular help with their sexual feelings, needs, and wishes.[9 10]

(4) Paediatric liaison. Children and young people with acute or chronic conditions on the hospital ward may not be able to maximise their use of the skilled care they receive because of emotional difficulties and distress. Individual treatment can help them make sense of their experiences and their feelings so that they can respond more positively to those around, staff, and parents.[11]

(5) Many children who have been abused have emotional sequelae. Emotional abuse can profoundly traumatise the child. Physical abuse, neglect, and sexual abuse usually involve considerable emotional abuse. The child's sense of self, self esteem, awareness of boundaries, ability to think their own thoughts, have their own feelings, own their own bodies, have all been attacked. Some of these children need individual treatment urgently. Other abused children, once in a safe place, want to settle into

a normal life and do not want at this time to talk about the abuse. Many of these children need help later, for example a sexually abused 7 year old girl may become very troubled at puberty, when she has a boyfriend, or when she marries or becomes pregnant and has the baby. She may need individual treatment at any or all of these transitions.[12–15]

(6) Children and young people with psychosomatic conditions where there may be emotional factors such as asthma, diabetes, or eczema can benefit from psychotherapy. There are also children and young people with quite severe problems such as abdominal pain to non-organic paralyses who have frequent hospital admissions and who can have considerable improvement with treatment.[16 17]

(7) Developmental delay can be generalised or specific. Children with overall delay often have emotional difficulties with autistic or psychotic features. Individual psychotherapy for these children is very specialised and the technique has needed modification, but some children can be helped to move forward.

Children with specific delays, language or numeracy delay, may have emotional factors which can be released. Children who are enuretic or encopretic can benefit, although many of them are difficult to help.[18–21]

(8) Children in transition in foster families or in adoptive families often have had very difficult experiences and are unable to use the new relationships because of the emotional pain, rage, and hurt confusion locked inside them. Individual psychotherapy can enable them to be freed up to engage appropriately with their new carers and can help avoid frequent breakdown of placements.[22 23]

(9) Adolescents have particular transitions and emotional turmoils. Becuase they are so volatile and fluctuating they can often make good use of a small number of sessions to make sense of their distress or confusion. Overdoses, anorexia nervosa, substance abuse, teenage pregnancy, leaving home, and moving to work or further education, can all lead to unresolvable difficulties. Some of the young people may respond to individual treatment but unlike young children they need to consent and bring themselves so the number taking advantage of this treatment is limited.[24 25]

Type of treatment

Individual psychotherapy is available from child and adolescent psychotherapists and child and adolescent psychiatrists if they have specialised in this therapeutic method. Child psychotherapists are generally psychologists, social workers, or teachers who have undertaken a postgraduate training.

Educational therapists are teachers who have undertaken further training in applying this treatment in the school setting with children with learning difficulties. Play therapists, nurses, and occupational therapists use some of the skills either with regular supervision by a therapist or after a postqualification course in therapeutic communication with children.

Treatment can be brief, for example five sessions offered to an adolsecent, or focused to work on a particular problem such as a bereavement or an inpatient admission. It can vary in frequency: generally it is once a week but for a very small number of children or adolescents who are very troubled it can be twice or three times a week. Very rarely indeed a child might be seen four or five times a week. Treatment may be time limited or may be open ended and reviewed at regular intervals and decisions on how to proceed then agreed.

Treatment is terminated when the child or young person ceases to be preoccupied with their conflicts or difficulties and better able to fulfil their potential and establish satisfying relationships. Improvement can continue for up to two years after treatment so the precise moment when to stop is still a matter of clinical judgment. Young people often vote with their feet and they decide when treatment will cease. Young children stop coming because the carer finds regular attendance difficult or continue coming for too long because the parents long to have their child 'transformed'. The work then has to shift into helping parents accept their child's condition. For treatment to be sustained most carers need regular contact with a worker to feel part of and involved in the treatment and to share their concerns. Children and adolescents recover more quickly and in general it is consolidated faster if the carers are actively involved with a worker exploring their part in the interactional problems and to help them think about how they can facilitate their child.

Prognosis

It used to be thought that children 'grow out' of emotional difficulties even if conduct disorders were predictors of problems in adult life. It is now recognised that children and young people with emotional disorders or mixed emotional and conduct disorders go on to have emotional and relationship problems in adult life. Therapeutic interventions can change this.[26]

Children and young people are generally resilient, many of them cope and can use resources available, for example a telephone help line, a professional, a teacher, their general practitioner or someone in the family, extended family, a friend, or a neighbour. But many pay a price in later life, children in divorcing families are more likely to divorce themselves, sexually abused children have relationship difficulties and mental health problems. Children unable to learn because of emotional problems do not achieve and can have frustrated and unsatisfying lives. It is not always the life events that are obvious which cause the problem, but whether the child has internal emotional strength, had good enough parenting, that is whether the current difficulty comes on top of pre-existing vulnerability. It does seem increasingly clear that without help troubled children become troubled adults in dysfunctional families. Of course, if a child is subject to a particular stress or a disaster then this may adversely affect the most robust of children and leave them with a post-traumatic stress disorder.[27]

Evidence that treatment is beneficial

Outcome studies are sparse and more are currently being undertaken. Previous studies tended to be global and now that projects are looking at which treatment for which problem with which child and which therapist, the benefits are emerging, showing that therapeutic interventions do bring immediate and long term benefits.[28–30]

Can it be practised by paediatricians?

Many paediatricians are very effectively communicating with children about their feelings. Winnicott in his therapeutic consultations with children showed how effective these contacts can be.[31] Some paediatricians undertake a course on therapeutic communication with children, but to provide regular treatment for some of the very troubled children would not make sense. A non-medical therapist would more appropriately provide this intervention linking with the child and adolescent psychiatrist.

Specialised training is needed

Individual psychotherapy requires assessment skills and communication skills. But it also requires enormous reserves of understanding, compassion, firmness, resilience, humour, courage, perseverance, and awareness of oneself and one's own competence, authority, and appropriate professional behaviour. To achieve this a very thorough in depth training is required.

When children and young people expose themselves to the therapist they can be very vulnerable, their feelings and their pain make them easily open to exploitation, and a therapist who lacks personal awareness may all too easily use the child or young person to meet their own emotional needs. An essential aspect of any training is that therapists must be aware of their own experiences and how their own lives have affected them, so that they know when they might respond appropriately.

Inappropriate treatment

If a child or young person has a particular external reality—moving to another area, transferring to boarding school, about to take GCSE exams—it is not appropriate to embark on an intense piece of work. Opening up very painful, distressing areas when there is no time to work them through or when the child or young person must go outside and function can be damaging. A therapeutic consultation would be the right way to proceed in such a situation.

There are also dangers if therapists find themselves out of their depth and unable to cope with a child's rage, pain, distress, or desperate need for affection. The therapist needs to be very clear about what is treatment and what is parenting to avoid behaving inappropriately. Suicidal young people or children experiencing abuse all need to be placed somewhere safe and be adequately parented or cared for; therapy can never replace parenting or provide monitoring. In cases that involve physical illness, acute or chronic, it is important to work with the general practitioner or paediatrician.

Services across the UK

Skilled individual psychotherapy was restricted to the four Thames regions. However, in the last 10 years there have been attempts to move out of London and there has been a blossoming of interest around the country. Training centres now exist in Edinburgh, Leeds, and Birmingham and courses are run in Bristol, Cardiff, Manchester, Liverpool, Newcastle, Oxford, and Cambridge. Trainees are also travelling from other cities to centres so that there are more services available. However, there is still a long way to develop before it will be possible for there to be adequate cover of even one centre per region. Child and adolescent psychotherapists and child and adolescent psychiatrists with a special interest are committed to developing this specialty.[32]

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Chinese paralytic syndrome

Diseases which appear to be confined to a single country are important not only because of their significance within that country but also because they often pose tantalising questions about basic mechanisms of pathogenesis relevant to all countries (think of kuru). Every year in the summer months in northern China there occurs an outbreak of a Guillain-Barré-like syndrome which affects mainly children but also some young adults. At the Beijing Children's Hospital the neurology service occupies one ward but every summer it overflows into two or three wards. More than a thousand cases have been described in the last 12 years. In just two weeks in August 1990, 36 cases were identified in two centres, Beijing and Hebei, and they were studied with the help of neurologists from Johns Hopkins Hospital. The findings have been reported in the *Lancet* (Guy M McKhann and colleagues, 1991;**338**:593–7).

All patients were from northern China and over 90% were from rural areas. Their ages ranged from 15 months to 37 years with a median age of 7 years. All had been vaccinated previously against poliomyelitis. Almost half described a prodromal illness within four weeks of the start of the neurological illness. At the onset of paralysis they were afebrile. Weakness began in the legs and was symmetrical and ascending to affect upper limbs, swallowing, and breathing. Thirty percent needed respiratory assistance. Maximum paralysis occurred usually after about six days and recovery began on average at about 16 days. Marked weakness of the flexor muscles of the neck with resistance to passive neck flexion was characteristic. Sensory loss was not a feature and neither was muscle tenderness or pain but there was often pain in the neck and back. There was no pleocytosis but protein in the cerebrospinal fluid was raised (above 0·45 g/l) in 15 of 26 samples. Electrophysiological studies showed normal sensory action potentials and motor nerve conduction velocities but reduced compound muscle action potentials and denervation potentials in the five patients who had electromyography done. The site of the disease process is uncertain. The authors interpret their electrophysiological findings as indicating dysfunction at either distal motor nerve terminals or anterior horn cells but point to the raised cerebrospinal fluid protein as suggesting disease at the proximal parts of the motor nerves or at the anterior horn cells.

The main differences between this disease and Guillain-Barré syndrome are its seasonal predilection and epidemicity, its occurrence predominantly in rural areas, the absence of sensory loss or of neurophysiological disturbance in sensory nerves, and the absence of electrodiagnostic evidence of a demyelinating neuropathy. The disease lacks many of the clinical features of poliomyelitis, all the children had been immunised against that disease, and poliovirus has not been recovered from their stools.

So it's not Guillain-Barré syndrome and it's not polio. What is it? So far no infective or toxic cause has been found though neither can be excluded. A poliomyelitis-like illness with fever and haemorrhagic conjunctivitis has been described in children in India and linked with enterovirus 70. It's not that. Something similar to the Chinese syndrome was described in Mexican children in 1969 but whether it was the same is uncertain.

So it remains an unsolved medical detective story even after the Hercule Poirots of Johns Hopkins have been called in. Fortunately the prognosis seems quite good on the whole, although a 3 to 5% mortality is quoted.

ARCHIVIST

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PERSONAL PRACTICE

Management of chronic constipation

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The management of chronic constipation in childhood has a number of problems and challenges for the paediatrician. It is seldom clear from the first contact with the child and family whether physical or psychological factors are paramount. Experience of managing a large number of such children has shown that most childrens' defaecation problems persists as a result of an intricate weave of a number of primary, secondary, physical, and psychological factors. Embarking on a single minded approach by the doctor may lead to a tightening of this knotty problem and subsequent loss of confidence and compliance. One of the objectives of this paper is to share some of this experience and define some of the features in the histories and the clinical examination which indicate the need for a particular emphasis in management.

Defining the terms

Throughout this paper the following terms are used with these meanings:

Constipation:	delay in defaecation[1] leading to distress (which may include anal or abdominal pain, overflow soiling, anorexia);
Soiling:	the escape of stool into the underclothing;
Encopresis: :	the passage of normal stools in abnormal places.

General principles of management

- Chronic constipation is important to treat in childhood because obstructive constipation in the young child will interfere with the child's physical development and overflow faecal soiling in the older child will have a destructive effect on self esteem and confidence.[2] Constipation may also complicate other childhood illness especially urological and neurodevelopmental problems.
- It is important to accept that the course is likely to be protracted and subject to disappointing relapses that demoralise all those involved.
- It should be recognised that every child has an individual weave of the factors and processes that both initiate the constipation and cause it to persist.
- Management is likely to involve a wide team of professionals who should share the same conceptual model of the child's problem in common with the child and family.

It is worth considering the stages in a typical case of constipation and its evolution as the child grows older:

(1) Difficulty with passing hard dry stools noted on weaning from breast to formula feeds at 6 months of age.

(2) Occasional delay of 2–3 days occurred and then the large stool was passed with considerable straining and passage of some fresh blood.

(3) Delays increased to one week or longer as child learned to avoid defaecation.

(4) Some overflow faecal soiling occurred which further irritated the anal skin.

(5) Attempts to pot train failed and parents added anger to frustration and anxiety.

(6) Fear of painful defaecation became augmented by the 'terrible 2s' with wilful rejection of parents' pleas to defaecate before the stool was so large that it hurt.

(7) The retained faecal mass in enlarged (and enlarging) rectum became physically larger than anal (and even pelvic) outlet which led to continuous soiling, hiding when sensation of imminent defaecation occurred, occasional massive but still incomplete rectal evacuation occurred and blocked the lavatory but yielded a few days of remission from soiling but reinforced the fear of defaecation due to fear of anal pain.

(8) Persistent soiling led to teasing and hostility.

(9) Recurrent failures of treatment regimens led to loss of confidence and compliance and then demands for more and more extreme treatments.

(10) Persistent failure of continence led to dissociation and the tendency to encopretic accidents even when the constipation came under reasonable control.

(11) Teenage improved vigilance and high social sanctions against incontinence increased treatment compliance and eventual improvement.

This can be considered diagrammatically with the related differential diagnosis and associated causes (fig 1).

Detecting the factors

POOR FOOD, FLUID, OR FIBRE INTAKE

Evidence for poor food, fluid, or fibre intake may be obscured by the infant appearing to be content with the feeding regimen but passing dry, hard stools as a result of the relative deficiency of fluid. A full daily intake assessment often provides evidence of poor or faddy intake. I found in surveying 488 children with constipation that 48% had some or many fads (compared with 29% in the National Child Development Survey (NCDS)[3]) and a poor appetite described in 47% (compared with

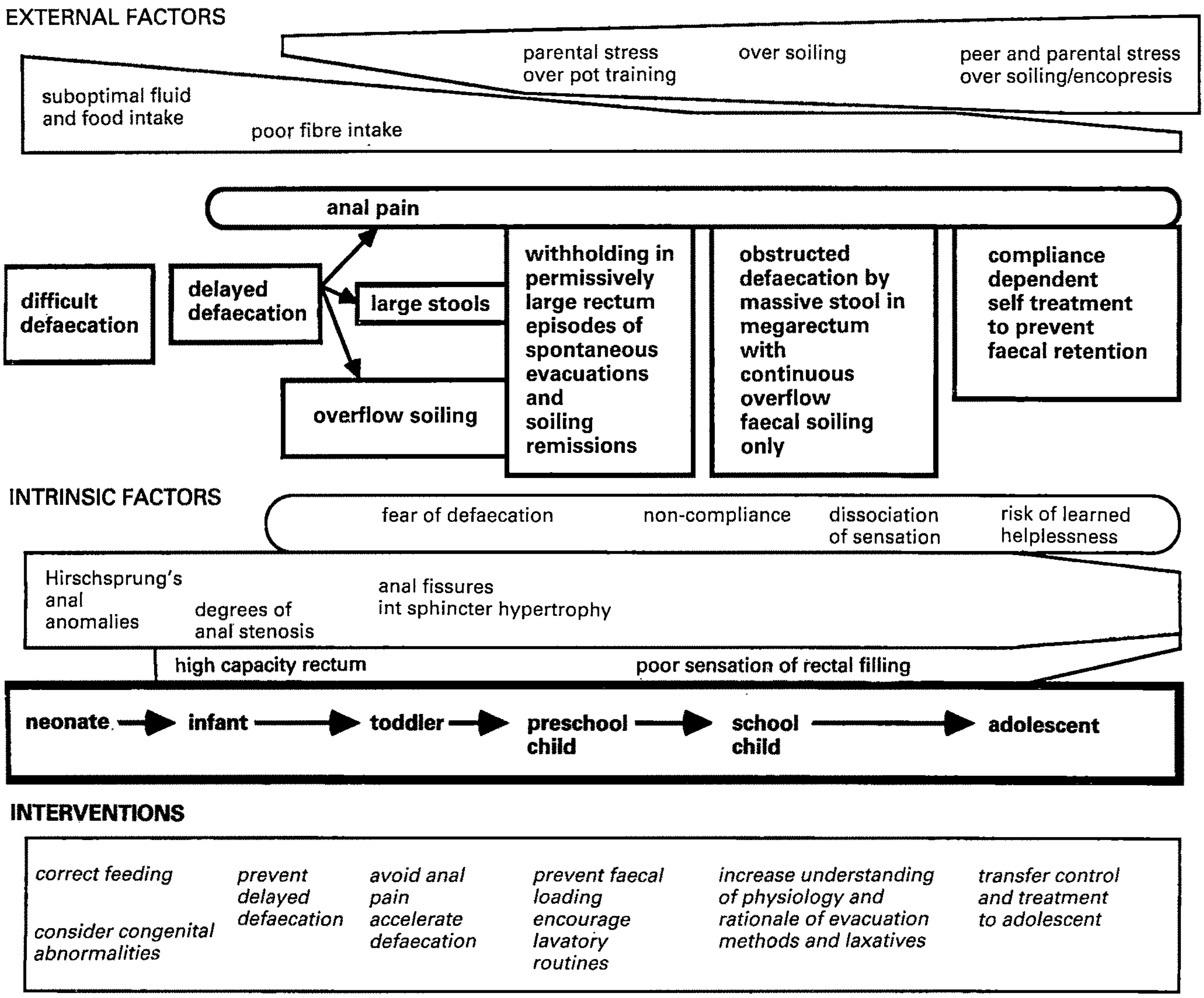
EXTERNAL FACTORS
suboptimal fluid and food intake
poor fibre intake
parental stress over pot training
over soiling
peer and parental stress over soiling/encopresis
anal pain
difficult defaecation
delayed defaecation
large stools
overflow soiling
withholding in permissively large rectum episodes of spontaneous evacuations and soiling remissions
obstructed defaecation by massive stool in megarectum with continuous overflow faecal soiling only
compliance dependent self treatment to prevent faecal retention
INTRINSIC FACTORS
fear of defaecation
non-compliance
dissociation of sensation
risk of learned helplessness
Hirschsprung's
anal anomalies
degrees of anal stenosis
anal fissures
int sphincter hypertrophy
high capacity rectum
poor sensation of rectal filling
neonate
infant
toddler
preschool child
school child
adolescent
INTERVENTIONS
correct feeding
consider congenital abnormalities
prevent delayed defaecation
avoid anal pain
accelerate defaecation
prevent faecal loading
encourage lavatory routines
increase understanding of physiology and rationale of evacuation methods and laxatives
transfer control and treatment to adolescent

Figure 1 Evolution and interaction of factors in chronic constipation in childhood.

NCDS incidence of 16% of poor appetite). Of my 47% with a poor appetite about half of these improved after they had passed their retained stool. This provides the evidence for the vicious cycle of poor intake, faecal retention, poor appetite.

CONGENITAL ABNORMALITIES OF THE ANORECTUM

The aptly named Soranus recommended to the ancient Romans that all newborns should have a finger passed through the anus soon after birth to divide the anorectal membrane.[4] More modern authors also support the view that anorectal rings in infancy are common.[5] This invasive examination should be reserved for those babies in whom there is a suspicion in the history that a degree of obstruction is being caused. In my survey 7% of the constipated children had delay in passage of meconium in the neonatal period and 13% had passed ribbon stools. Others have reported early onset constipation due to subtle anal abnormalities that have eluded early diagnosis.[6] However it is the spectre of Hirschsprung's disease which, if the diagnosis is neglected, can lead to necrotising enterocolitis or perforation, which hovers over the problem of early onset constipation. Other features which suggest that the constipation may be due to Hirschsprung's disease in addition to delay in passing meconium are: (i) failure to thrive, (ii) vomiting, (iii) appreciable abdominal distension, (iv) alternating constipation with diarrhoea, (v) an explosive gush of faecal material on withdrawing the examining finger from the rectum, and (vi) relatively little overflow faecal soiling for the degree of faecal retention in the older child (note that soiling may occur but the volume is less).

We found approximately 10% of severely protracted constipation in children referred to us initially was caused by Hirschprung's disease.[7] More recently, even with increased awareness of the condition the incidence of Hirschsprung's disease in those referred is 3% and many of these children are indistinguishable from those with megarectum who have normal acetylcholinesterase staining on their suction rectal biopsy specimens.

ASSESSING THE ROLE OF ANAL PAIN

I found a history of pain on defaecation in 74%, blood in the stool in 55%, and a history of a previously diagnosed anal fissure in 17%. This understandable motivation for a child to try their utmost to avoid defaecation, which they have learned is painful, is central to the initiation and the persistence of this cycle of problems. Anal fissure is one of many causes of painful defaecation, others include the passage of large, hard stool from the megarectum, anal soreness due to persistent soiling. Other causes are group A streptococcal perianal infection (a grossly underdiagnosed infection: every perianal skin swab we have taken in recent months when the skin has been red with evidence of purulent exudate has been positive, indicating a course of penicillin in addition to stool softeners), skin diseases (lichen sclerosis et atrophicus, epidermolysis bullosa, severe eczema (with or without milk intolerance)), and anal abuse. (Although the anal signs of abuse may be mimicked to some degree by chronic constipation it should not be forgotten that constipation can be caused by the avoidance of defaecation as a result of the anus being sore as a result of abuse. It should also be remembered that a child may perceive rectal examinations and rectally administered enemas and suppositories as abuse especially when force or coercion is used.)

ASSESSING THE DEGREE OF MEGARECTUM

Evidence which supports the theory that the child has a large capacity rectum can be obtained from detailed anorectal manometry studies on the bowel.[8 9] These confirm the belief that chronically constipated children have high capacity rectums with relatively insensitive anorectal inhibitory reflexes even where Hirschsprung's disease has been excluded. In assessing the individual child a history of appreciable delays in defaecation, of passing massive ('lavatory blocking') stools, and a palpable mass in the abdomen are useful features. I found that 37% opened their bowels less frequently than weekly and in a half of these the delays were greater than two weeks between stools. Altogether 45% claimed to be passing only massive stools and only 14% claimed never to have produced a massive stool. Examination of the abdomen in the chronically constipated child usually demonstrates a degree of faecal loading felt central, extending up to as far as the xiphisternum in some children. I found that 25% had stool palpable but below umbilicus, 20% to the umbilicus, 21% to between the umbilicus and the xiphisternum, and 33% who had no stools palpable in the abdomen had either recently passed a 'megastool' or had soft faecal loading of their megarectum where the upper limit was not possible to define with ease. There is an important lesson to be learned from this group because failure to appreciate the degree of retention in these children, when there is overflow faecal soiling, can lead to erroneous treatments to further delay effective defaecation or lead to misdirected psychotherapy. It is with this group of soft retainers that inspection of the pattern of lower abdominal distension may give the clue to rectal loading. Here an abdominal radiograph may confirm the retained stool. Abdominal radiographs may be very valuable as an education device to reinforce the message about the faecal loading especially when the children are unable to palpate the extent of the loading themselves either because it is so soft or because they are unable to understand what they are palpating. This clear image of the retained stool goes a long way to demystifying the bowel problem and may be very helpful in the parallel psychological management.

ASSESSING THE ASSOCIATED FAECAL INCONTINENCE

The difficulty and delay in defaecation may not trouble the child as much as the stress caused by soiling and the social response to this. Often the presenting symptom is constipation and defaecation avoidance in the preschool period but the overflow soiling increases in importance as the child approaches the years of formal schooling. In my experience it has been the soiling rather than the constipation that has fuelled the desire for further opinions on the bowel problem. It is not surprising that the average age of referral to my mainly tertiary service is 5·5 years.

The soiling frequency pattern supports the idea that soiling is mainly an involuntary escape of loose or semisolid stool around the retained stool in the megarectum. Twenty nine percent of my patients with constipation had no problem with soiling, whereas 35% soiled discontinuously (remission of soiling when the large retained stool was eventually passed), and 36% soiled continuously (probably indicating that the faecal mass in the rectum was never fully evacuated). As expected the presence of a distressing and embarassing condition such as soiling leads to or exacerbates psychological problems.

ASSESSING THE PSYCHOLOGICAL FACTORS

As summarised in fig 1 the psychological factors can be conveniently divided into the *extrinsic* (family and society) and *intrinsic* (feelings, behaviour reactions, and beliefs). The fear of defaecation is understandable when the reinforced knowledge that the activity is bound to be painful is compounded by parental pressures to conform to what they see as the most helpful and protective course. This clash of understanding and conflict of autonomy can be most easily illustrated by this dialogue:

> *Child:* 'Every time I pooh it hurts, so I am not going to do that again'
>
> *Parent:* 'You must sit there and open your bowels because if you put it off any longer it will be even more painful'

The parents' logic, although correct, is lost on the child and the tension rises. I have evidence for this in my study as 62% of the children have regularly refused to sit on the pot or lavatory and 69% of parents have at some stage in the evolution of the problem used coercion of some form (this was carried out by mothers in 60%, father in 8%, and both in 32%). So it can be seen how the child's fear and the parents response interact to produce another vicious cycle. When unpleasant or coercive medical management is added to this formula it is not surprising that the difficulties escalate. The use of invasive anal treatments before referral in my patients was 63% for suppositories and 38% for enemas.

My initial observation of the child and family at first consultation included a question to the parents on how they perceived the child's behaviour. They responded as normal or sociable 61%, aggressive 13%, and shy 26%. My initial observation of the child gave similar figures for normality and shyness (60% and 21% respectively) but I noted aggression in only 2% in the atmosphere of the consulting room. Psychotherapy had been or was taking place also in 15% (compared with NCDS incidence of 1%).

In the older child the fear of defaecation seems to be eclipsed to the embarrassment and fear of exposure related to the soiling. Both these fears undermine compliance and in the older child increase the dissociation which so aggravates their elders. Another dialogue may clarify this:

Child: 'I don't need to go to the loo, I haven't soiled, and I feel fine'

Parents: 'I can smell it, go straight up and change—and don't just hide your messy pants—I found six pairs stuffed behind your radiator yesterday—you're deliberately trying to annoy me'

Child: 'I can't help it—I just want it to go away so I can be normal'

Parent: 'Just try harder to keep your pants clean, and do as you're told'

It is well worth exploring the belief scheme that the child and family have about the relationship between defaecation and soiling and where the 'trying harder' should be aimed. Providing a basic diagram of the filling rectum activating both inhibitory reflexes (which will relax the internal anal sphincter) and the sensory imput to the brain (which can initiate external sphincter responses if sensation of urgency is perceived) will help. If there is reasonable evidence of the megarectum from palpation, abdominal radiography, or even anorectal manometry the involuntary nature of overflow soiling, the likelihood of diminished rectal sensation of filling, and the difficulty of being able to pass megastools without help are readily understood. This understanding is paramount in the management of constipation at any age and supplying relevant explanatory pamphlets is helpful.[10] In the adolescents it is vital as it will help them to focus on the appropriate activity (emptying the rectum fully) and exonerate them for the years of soiling with the associated guilt and blame. In the younger child a clear understanding of the factors may avoid a number of the secondary psychological problems in the child and family and aid compliance as the child understands the logic of some of the treatments which might be relatively unpleasant and time consuming.

Logical treatment for constipation and its complications

Developing a shared model of the interaction of the factors may involve consideration of many of the factors above which should be clear from a full history, examination, and perhaps abdominal radiograph. If features of Hirschsprung's disease are present then suction rectal biopsy for acetylcholinesterase positive nerve excess should be requested.[11]

Evacuation of retained faeces in the large rectum is best carried out by softening the mass sufficiently with docusate sodium (Dioctyl paediatric syrup, Medo) then using sodium picosulphate elixir (Laxoberal, Windsor or less acceptably Picolax, Ferring) as a single dose provided the faecal mass is of a size which could be physically passed through the pelvic outlet and anus. If there is doubt about this then a more prolonged course of docusate sodium with its detergent like activity may permit the picosulphate treatment later. If picosulphate is ineffective even after repeating an adequate dose further success may be achieved by using a polyethylene glycol solution such as Golytely (Seward)[12] or Klean-Prep (Norgine) (although high fluid volumes are required and, if nasogastric tubes are the only effective method of administration, it would be kinder to use alternative means). If these oral methods are ineffective or impossible to administer the use of microenemas or phosphate enemas can be considered provided the child understands and can cooperate with them or can be given sufficient sedation to avoid the stress.

If the enema procedure is impossible, ineffective, or if the faecal mass is persistently too large to pass despite a lengthy course of docusate sodium, or if there are signs of acute impaction, an evacuation under a general anaesthetic should be performed. An extra benefit that can be gained from the manual evacuation under general anaesthetic is that the opportunity to perform a vigorous anal dilatation can be taken. This will weaken any increase in the activity of the internal anal sphincter (secondary to the prolonged faecal retention leading to rectal smooth muscle hypertrophy) seen on anorectal manometry.[8 9] Once the rectum is clear from the accumulation of old stools, steps must be taken to avoid a new build up.

Maintenance treatment involves using both bulk laxatives such as lactulose or methylcellulose tablets (Celevac, Boehringer Ingelheim) as well as regular stimulant laxatives such as senna (Senokot, Reckitt and Coleman). Regular senna given once a day or alternative days is helpful in stimulating an episode of defaecation approximately 24 hours later. With a sufficient dose the reluctant child may not be able to prevent the stools from being passed and the older child may have a more complete defaecation at a convenient time for spending a period in the lavatory. Once the senna regularity is achieved it is vital that the medication is continued for long enough to avoid a relapse. In my study currently in progress, stopping active laxatives too soon is the commonest cause for relapse.

Figure 2 shows the length of time my patients have spent regularly taking stimulant laxatives. This is in agreement with traditional teaching that children with chronic constipation rarely require less than a year on stimulant laxatives.

If periods of reaccumulation occur then it is essential to repeat the evacuation procedure. It

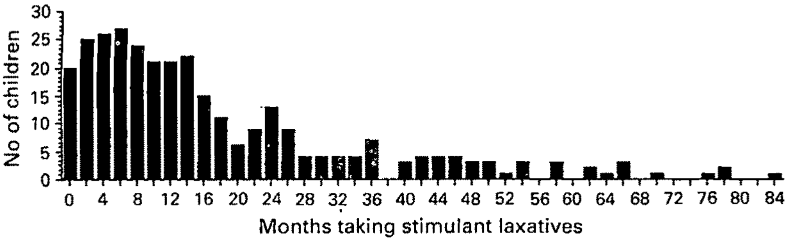

Figure 2 Duration of stimulant laxative treatment.

may be helpful in children who frequently relapse to have a boost in the laxatives by having regular weekend sodium picosulphate provided they are warned of the loose stools in advance of important social activities.

Frequent relapsers may benefit from an *anal dilatation or partial internal anal sphincterotomy*[13] when there is evidence of internal anal overactivity. The table show some data from 230 children with severe protracted constipation treated in my clinic treated over a four year period.

It should be stressed that parallel psychological help is vital for approximately half the children presenting with protracted constipation. In children with hugely dilated megarectums other abnormalities of the myenteric plexus other than Hirschsprung's disease may be involved and this is an area of developing interest.[14] Only by clear understanding of the abnormalities of the myenteric nerve plexi will the children with apparently untreatable constipation be clearly separated from those in whom the treatment regimen has been subtly sabotaged either as part of a Munchausen by proxy syndrome or where the family dynamics have become so dependent on the child's bowel problem that resolution of this appears too hazardous to the family members.

These two extremes facing the paediatrician demonstrate how important it is to have a correct appreciation of the factors involved in the condition as well as access to specialised teams embracing specialised paediatrics, psychiatry/psychology, surgery/histopathology, and nurse specialists when the constipation becomes complicated.

Data from 230 children seen over a four year period

	No (%) of children
Off laxatives	
No anal dilatation	47 (20)
Rapid response to anal dilatation	32 (14)
Slow response to anal dilatation	58 (25)
Rapid response to sphincterotomy	7 (3)
Slow response to sphincterotomy	6 (3)
Needed anal dilatation after sphincterotomy	12 (5)
Still on laxatives after four years	28 (13)
Failed to attend to complete regimen	40 (17)

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CURRENT TOPIC

The provision of safe surgery for children

John D Atwell, Paul M Spargo

In 1977 a grant was given to the Association of Anaesthetists of Great Britain and Ireland by the Nuffield Provincial Hospitals Trust in order to carry out a confidential inquiry into deaths associated with anaesthesia. After this study a recommendation was made that future epidemiological studies should involve both anaesthetists and surgeons. The most recent report studied the deaths of children under 10 years of age within 30 days of an operation.[1] Confidentiality was assured and the patients who died were subjected to an independent review by surgeons and anaesthetists. In this survey 417 deaths occurred of whom 150 were non-cardiac patients and it was possible to review in details 102 of these patients. Seventy five per cent of these patients had been admitted as an emergency.

The findings and recommendations of The National Confidential Enquiry into Perioperative Deaths (NCEPOD)[1] are of vital interest to anyone responsible for the care of children. Two of the six recommendations are particularly relevant, firstly, '*Surgeons and anaesthetists should not undertake occasional paediatric practice*' and secondly, '*Consultants who take the responsibility for the care of children (particularly in District General Hospitals and in single surgical specialty hospitals) must keep up to date and competent in the management of children*'. No attempt was made to quantify or define the term 'occasional paediatric practice' and aspects of this will be discussed in this paper. It is therefore appropriate to consider the deficiencies highlighted by the report and some potential remedies.

As surgeons, anaesthetists, and paediatricians we are primarily concerned with the quality of care required for our patients. Infants and children requiring surgery should be operated upon with a minimal risk to life, few complications, and as little disturbance to the family unit as possible, that is, '*safe anaesthesia and surgery*'. The British Paediatric Association is concerned about audit, which has been defined as 'the systematic critical analysis of the quality of medical care, including the procedures used for diagnosis and treatment, the use of resources and the resulting outcome for the quality of life for the patient'.

Anaesthesia

There are no data comparing paediatric anaesthetic morbidity in the district general hospital with that in the regional paediatric unit. However, there are a number of large surveys of perioperative complications after anaesthesia and surgery in children (notably from the UK, France, and Canada). In the light of these studies and the infrequent exposure of most anaesthetists to children, a case can be made for the centralisation of paediatric anaesthetic (and intensive care) services.

Anaesthetic problems occur most frequently in children under 3 years of age.[2] Anaesthesia in the older child is similar to that in the adult. Several large studies have confirmed the high incidence of perioperative anaesthetic complications in the neonatal and infant age ranges. In a prospective survey from France, a total of 40 240 anaesthetics were administerd to children less than 15 years, 2103 (5%) involving infants (younger than 1 year). Twenty seven major complications (defined as a fatal or life threatening accident or any incident producing severe sequelae, which occurred during, or within 24 hours of, anaesthesia) were recorded; this is an incidence of 0·7 per 1000 anaesthetics. Nine (of which four were associated with cardiac arrest) were observed in infants. The risk of complications was significantly higher ($p<0·001$) in infants (4·3 per 1000) than in children (0·5 per 1000). Of the nine events in infants, seven were respiratory problems (airway mismanagement, complications of intubation, aspiration, postoperative respiratory depression). Most of the complications seemed avoidable.[3]

That the younger age groups are the most vulnerable is confirmed by another study from Canada of 29 220 patients under 16 years of age. Neonates had the highest rate of adverse events both intraoperatively and in the recovery room. Infants (1 month–1 year) had the next highest incidence of major perioperative events, which included respiratory and cardiovascular problems, surgical complications, and death. The intraoperative death rate in this age group was eight per 10 000 and the early postoperative death rate (within three days of operation) was five per 10 000, which was the highest in any age group after the neonatal period. The authors commented that the majority of children were healthy and 70% had no preoperative medical conditions.[4]

One of the recommendations of the report of NCEPOD, which looked at the causes of death in children within 30 days of surgery, was that surgeons and anaesthetists of adults should not undertake occasional paediatric practice, yet it has been estimated that 70% of children under 3 years are anaesthetised in adult hospitals.[5] In the same editorial it was estimated that this represented one or two cases per consultant anaesthetist per week. Figures from our own

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unit confirm this: 2000 children under 3 years of age per year (and 2900 children under 5 years of age per year) mean one or two cases per consultant per week and/or one or two cases per trainee per week. In the 1989 NCEPOD report 2109 anaesthetists were asked how many children they anaesthetised each year and 80% stated that they anaesthetised less than one child in the age group 6 months to 3 years per week (40% anaesthetised only one or two per month). Ninety per cent anaesthetised fewer than one child in the under 6 months age group per week. Even in a large district general hospital in the under 3 age group an average of only two cases are anaesthetised per consultant per month (0·7 cases under 1 year per consultant per month). Such small numbers are insufficient to maintain skills or allow training of junior staff[6] and they are also insufficient to allow back up staff (theatre nurses, operating department assistants, and recovery staff) to gain adequate experience. The adult intensive care of the same district general hospital admitted 25 cases under 13 years of age in the year studied (three infants and four children 1–3 years old).

Avoidance of complications is primarily a matter of training and experience.[7] From the preceding discussion there is evidence that there are insufficient patient numbers to acquire and maintain paediatric anaesthetic skills. Centralisation of paediatric surgery and intensive care would improve this situation and may lead to a reduction in the distressingly high morbidity and mortality observed in the younger age ranges.

Surgery

The general surgery of childhood can be conveniently subdivided into three different age groups: (1) neonatal surgery (under 1 month of age), (2) the surgery of infancy (under 1 year of age), and (3) the surgery of the preschool child (under 5 years of age). In this paper the surgery of the older child is not considered as in some respects it is similar to that in adults. Naturally a surgical admission may be as an emergency or for an elective procedure.

There is no doubt that we are in an era of increasing specialisation within medical and surgical paediatrics. Ophthalmic and ear, nose, and throat surgery and orthopaedics are examples of 'in line specialties' whereas the 'general' paediatric surgeon specialises within an age range. In recent times subspecialty groups are increasing in numbers, such as in urology and neurological and cardiac surgery—for example, in England and Wales there are now five surgeons who specialise in paediatric urology. As knowledge increases specialisation will gain further momentum that must be maintained if better standards of care for our patients is to be achieved.

(1) THE NEONATE

There is no doubt that the surgery of the newborn should be carried out either within regional neonatal surgical centres or within specialised units, for example, cardiac and neurosurgery.

Deficiencies have been discovered by NCEPOD[1] and these fall into two main categories. Firstly, surgeons have been operating outside their training and experience and secondly, the facilities for the full care of the neonate within some specialist units is far from ideal. This situation can be remedied by the appropriate referral of the newborn and the upgrading of facilities in some specialist units. The former is the responsibility of the referring paediatrician and the second is the responsibility of the specialist unit in conjunction with the local paediatrician. Only in this way will the overall care of the surgical neonate improve with a reduction in mortality and morbidity.

Transport of the sick neonate has always been a problem. There has been a tendency for neonatologists to refer neonates to a local surgeon rather than arrange a transfer to an appropriate neonatal or specialist unit.[1]

The antenatal diagnosis of a serious structural malformation such as a gastroschisis or congenital diaphragmatic hernia allows the transfer of the mother to an obstetric unit adjacent to the specialised surgical unit. Prompt surgical treatment with the minimum of disturbance to the neonate is therefore possible. This form of management has led to a reduction in the mortality of gastroschisis.[8] In other conditions, particularly those affecting the genitourinary tract, the mother and baby may be transferred after delivery in their local obstetric unit. Full urological investigations of the neonate can then be undertaken in the appropriate centre.

In some instances where transfer before delivery has not occurred the receiving unit should consider the development of an emergency team which could go out and organise resuscitation and transfer of the surgical neonate. This is very appropriate for the modern management of congenital diaphragmatic hernia. Close liaison between obstetrician, neonatologist, and paediatric surgeon will ensure the optimal management of the fetus.

(2) THE INFANT

If hernias are excluded there are two emergency surgical conditions which may occur in the first year of life: congenital hypertrophic pyloric stenosis and intussusception. These operations were considered suitable for the general surgeon. This situation has changed and there is a case to be made for the transfer of such infants to a regional centre unless the local general surgeon has had training and experience as agreed by the specialist advisory committees of the Joint Higher Surgical Training Committee of the Royal College of Surgeons.

(a) Congenital hypertrophic pyloric stenosis

This procedure has a mortality and a morbidity, usually wound infection, dehiscence of the wound, and perforation of the duodenal mucosa. The incidence of some of these complications in reported series from district hospitals and specialist units is seen in the table.[9–15] A study of this table will support the case for the referral of congenital pyloric stenosis to specialist units. There is a sevenfold increase in mortality

Reported series of treated pyloric stenosis in district hospitals and specialist centres. A comparison of the mortality between the two groups is significant ($\chi^2=3{\cdot}638$, $p>0{\cdot}05$–$<0{\cdot}1$). Results are number (%)

Author	*No of patients*	*Deaths*	*Perforation*	*Wound infection*	*Wound dehiscence*
Bristol and Bolton 1981[9]	78	None	9 (11·5)	7 (9·0)	3 (3·8)
Gray, *et al* 1984[10]	101	2 (2·0)	5 (4·9)	11 (10·9)	2 (2·0)
McDonald 1986[11]	47	None	10 (21·2)	3 (6·3)	2 (4·2)
Beynon, *et al* 1987[12]	100	1 (1·0)	3 (3·0)	14 (14·0)	5 (5·0)
Erikson and Anders 1991[13]	46	None	11 (23·9)	7 (15·0)	2 (4·3)
Total	372	3 (0·8)	38 (10·2)	45 (12·0)	14 (3·7)
MacKay and McKellar 1986[14]	222	None	Not stated	16	Not stated
Fitzgerald 1986[15]	607	1 (0·2)	Not stated	Not stated	Not stated
Total	829	1 (0·1)			

(0·8%:0·12%). The incidence of mucosal perforation at the operation is high (10·2%) with a range from 3%–23·9%. The reason for this is obvious when one studies in detail the findings in two of the reports.[11] [13] In the first study 47 patients were treated over a 10 year period by six consultants and four registrars, an average of 4·7 cases per year.[11] In the second study of 46 patients treated over a five year period 13 were operated upon by a consultant, 19 by a senior registrar, and 14 by a registrar after fellowship, an average of two or three cases a year for the consultant, four per senior registrar, and two or three by the registrars.[13] These are examples of occasional paediatric practice and so it is not surprising that the incidence of mucosal perforation was 21·2%[11] and 23·9%[13] respectively. There have been two reports with a low incidence of this complication, one by a single general surgeon with one recognised perforation out of 90 patients[16] and another by a paediatrician with a single duodenal perforation out of 104 patients.[17] This demonstrates the excellent results which can be achieved by the concentration of the clinical material.

(*b*) *Intussusception*

Intussusception is an uncommon surgical emergency of infancy but associated with a significant mortality. In England and Wales 33 children died of this condition between 1984 and 1989. This was an improvement over the preceding six year period when 67 children died.[18] The median age of death was 7 months and was from two principal causes. Firstly, delay in diagnosis accounted for half of the deaths that occurred either at home or soon after arrival in hospital. The other causes of death were avoidable and related to inadequate intravenous fluid and antibiotic treatment, delay in recognising a recurrent intussusception, and inappropriate surgery. The sad thing is that most of these children were fit and healthy before the acute onset of an intussusception. Only one of these patients was under the care of a specialist paediatric surgeon and only then after transfer from another district hospital when the intially operating surgeon had failed in his assessment of the viability of the intestine which resulted in ischaemia, intestinal perforation, and a multisystem organ failure. Any paediatrician undertaking the correct management of intussusception by hydrostatic reduction needs to ensure that the radiologist has sufficient paediatric training *and* that surgical expertise exists for the 20% who may require it.

(3) THE PRESCHOOL CHILD

The commonest causes of an admission to hospital under 5 years of age are inguinal hernia, undescended testes, abdominal pain, and head injuries or other trauma. Some of these conditions such as inguinal hernia and undescended testes can be treated as an elective day case admission. Others may present as a surgical emergency (inguinal hernia, acute appendicitis) with an increased risk to the child.

(*a*) *Inguinal hernia*

The incidence of inguinal hernia varies between 2–4% in the full term infant but increased to 30% in the premature infant under 1000 g birth weight. Incarceration is a complication with the highest incidence in the first three months of life. It therefore follows that surgical repair of the hernia should be undertaken as soon as possible after its diagnosis. In a series of 511 infants under 1 year of age, 158 had become incarcerated but only seven required an emergency operation; the remainder reduced after sedation and postural reduction.[19] In two the testes were undescended and on follow up only two patients had evidence of testicular atrophy, an incidence of 0·4%. This is an example of the high standards obtainable in a specialist centre. In the NCEPOD report five infants died from complications related to surgery and anaesthesia after treatment of an inguinal hernia.

(*b*) *Undescended testes*

An undescended testis only warrants an emergency operation if complications occur such as torsion or incarceration of an associated inguinal hernia. These are relatively rare complications, thus the majority of patients are treated as elective day case admissions. It has been recommended that surgery should be undertaken before 2 years of age if an improvement in fertility is the aim of treatment.[20] Orchidopexy in boys under 3 years of age requires considerable surgical expertise if complications such as damage to the vas deferens, failure to place the testis in a satisfactory position in the scrotum, and atrophy of the testis are to be avoided. Few reports appear in the literature of the morbidity of an orchidopexy,[21] [22] but in one series of 142 orchidopexies atrophy was found in 31% and an unsatisfactory result in 35% when reviewed five years after surgery.[21] In a similar review from the same centre nine years later and after the appointment of a general surgeon with interest, training, and experience in paediatric surgery the incidence of atrophy was 9·4% of 128 orchidopexies. This single example highlights the importance of appropriate training and experience in performing a routine standard, and in the past a general surgical operation.

(*c*) *Acute appendicitis and abdominal pain*

Acute appendicitis is fairly uncommon in the child under 5 years old. In older children the acute abdomen is a common cause for an emergency hospital admission of whom approximately 50% will need a laparotomy.[23] Acute appendicitis has a mortality particularly in the very young. Two hundred and four children died from acute appendicitis from 1963–7,[24] and the mortality was eight times higher in those aged less than 5 years of age compared with those aged 5–14 years.

NCEPOD

The first conclusion of the inquiry was that '*The prudence of the occasional surgeon undertaking complex childhood surgery must be questioned*'. However, five deaths occurred in infants with a strangulated hernia and in the eyes of a general surgeon and possibly a paediatrician this is not a complex procedure.

A second purpose or result of the inquiry was to determine the number of children operated upon by 5000 consultant surgeons in each year. The children were subdivided into three groups aged 0–6 months, 6 months–3 years, and 3–10 years. Only 39% of surgeons operated on more than 40 children per year under 10 years of age, that is, less than one per week.

Considering general surgeons in greater detail it was found that 12% never operated upon children, another 19% did not operate on children under 6 months of age, and another 32% operate on infants under 6 months of age but less than 10 patients per year. The only conclusion that can safely be drawn from this data is that '*A rethink is necessary for the provision of general surgical services to children*'.

Finally considering the care of children within special surgical units (for example, neurosurgery, burns, cardiothoracic and plastic surgery) it was found that these infants and children were often '*denied the care of paediatricians and specialist paediatric nurses*'. Similarly it was also reported that general surgeons were occasionally pressurised by enthusiastic neonatologists to operate upon patients outside their usual expertise rather than transfer them.

The future

From the data that has been presented and from the NCEPOD report it seems that changes are needed in the present system of management of surgical problems in the infant and young child. In Australia and the USA paediatric surgery is only undertaken by paediatric surgeons at all ages and the standard of care is very high. In this country the standard of care is high[1] but that does not mean that improvements are not possible. For example we have shown that there has been a considerable improvement in the mortality of intussusception in recent years.[18]

In the past incarcerated hernia, pyloric stenosis, and intussusception were considered general surgical operations that any surgeon could do. This must now be questioned. In addition to the data presented, it is also important to appreciate that many surgical trainees receive little exposure to the surgical care of infants and young children and the number of adult general surgeons able to operate on infants will therefore decrease.

One solution to this situation is that all the general surgery of the very young, that is, on those under 3 years of age, should be referred to specialist centres especially if the admission is an emergency rather than for an elective procedure. In most of these centres there will either be paediatric surgical and paediatric anaesthetic expertise available. The British Association of Paediatric Surgeons has suggested that transfer of patients under 5 years should be the eventual aim. In our own unit 60% of day case admissions for an elective general surgical procedure are under 5 years of age.

If this method of management is undertaken one has to determine whether the existing paediatric surgical units could cope with the increased work load. Taking pyloric stenosis as an example of an emergency with a 2 million population, the expected annual work load could be 100 patients, that is two patients per week. The figures for intussusception are about half this. The duration of hospital stay is now short (two or three days), thus this commitment would require at leat 300 bed days per year.

The vast majority of the elective surgery in the very young can safely be performed on a day basis, for example, inguinal herniotomies, orchidopexies, and circumcisions, especially with good back up in the community by paediatric trained district nurses.[25 26] A children's day surgical unit of six beds has the capacity to treat 50–60 patients per week, that is, up to 2000 a year. In our own children's day unit in Southampton 52% of admissions come from Southampton and its immediate environs and 48% are from further afield within the Wessex region. In fact with the efficient use of day beds our overall patient turnover has increased 330% since 1966 to 1969.

The NCEPOD report highlighted the risks and dangers of the 'occasional surgeon' but did not attempt to define the limits of such experience. This has been discussed under pyloric stenosis and intussusception. It depends upon the views about the value in concentrating experience.[27–29] In Liverpool when neonatal surgery was concentrated into a single unit the mortality fell from 75% to 25% within five years. A similar concentration for the general surgery of the child under 3 years of age should result in an improvement in mortality and morbidity.

Improvements in patient care can be achieved by improving facilities, for example paediatric surgical centres should have inpatient beds, day care beds, and five day stay beds. These facilities combined with paediatric community care would increase efficiency and patient turnover.

There is no doubt that audit of surgical results will eventually lead to an overall improvement in the care of the patient but surgical customs and prejudices will need to be overcome. We are in an era of increasing specialisation within medicine and surgery. On a personal basis one is competent to perform abdominoperineal resections of the rectum or prostatectomy in adults but one very much doubts whether the results would approach those achieved by a practicing colorectal surgeon or urologist. Our surgical aims must remain in trying to improve the standards of care which our young children need and deserve.

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LETTERS TO THE EDITOR

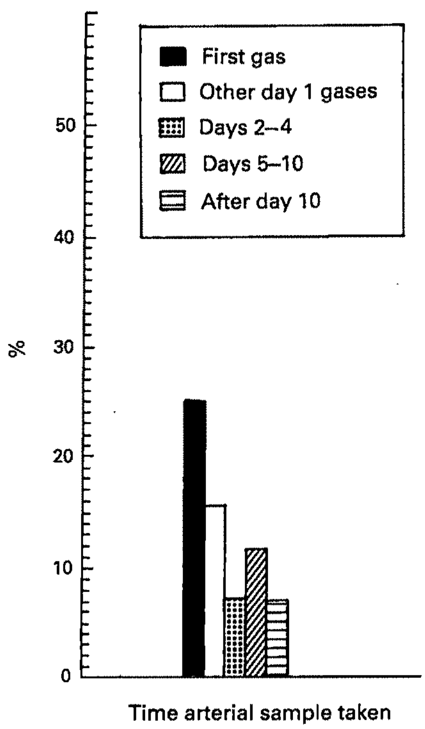
Neonatal hyperoxaemia

SIR,—Although hyperoxaemia is no longer considered the sole risk factor for retinopathy of prematurity,[1] litigants still frequently cite it as the cause, arguing that too much oxygen was given and that hyperoxaemia could have been prevented. In order to understand the timing and frequency of hyperoxaemia, we reviewed all arterial blood gases on babies <33 weeks' gestation who received supplemental oxygen for respiratory distress by headbox, continuous positive airway pressure or ventilation, and had repeated arterial samples. Before establishing an arterial line babies were nursed to maintain preductal transcutaneous oxygen tensions of 7–12 kPa, and thereafter to maintain similar arterial oxygen tensions (PaO_2).

A total of 1836 arterial samples were taken from 90 babies. Their median (range) birth weight was 1220 (480–2550) g and median gestation 29 (24–32) weeks. The median number of samples from individuals was 15 (2–170). On day 1, 452 (25%) samples were taken, 707 (39%) on days 2–4, 378 (21%) on days 5–10, and 299 (16%) thereafter.

Fourteen babies were excluded from the analysis because they died within 48 hours. They had a total of 94 arterial samples before they died, and only one had a PaO_2 $\geqslant$12 kPa. Among the other 76 babies, 64 (84%) had at least one PaO_2 $\geqslant$12 kPa, the level considered to be hyperoxaemic. Hyperoxaemia was most frequent at the first arterial sample, when 19 (25%) of babies had levels above the threshold.

Fifty two (16·5%) of the 315 other samples on day 1 had a PaO_2 $\geqslant$12 kPa, a higher proportion than any other day. A second peak was observed at days 5 to 10, when 44 (11·6%) samples were hyperoxaemic. We believe this reflected the tendency for PaO_2 to rise on constant respiratory support during recovery from surfactant deficiency. No period was free of hyperoxaemia, but the lowest prevalence was 7·0% (21 of 299 samples) after day 10 (figure). These trends were similar when thresholds of 14 and 16 kPa were used.



Percentage of gases at different time intervals when the PaO_2 was $\geqslant$12 kPa.

There is no universally agreed definition of hyperoxaemia in preterm infants. The upper limit of our target range was 12 kPa and was therefore the empirical definition. The level of 12 kPa is 4 SD above the mean (SD) PaO_2 of 7·9 (1·0) kPa in normal premature infants at 3 to 5 hours of age.[2] Thibeault *et al* did not record a PaO_2 $\geqslant$12 kPa in air breathing non-distressed babies of 1201–1600 g until day 12.[3]

If hyperoxaemia is causally related to retinopathy in some babies, it is crucial to know (a) when hyperoxaemia is most likely to occur and if it can be prevented, and (b) if the developing retina is susceptible to hyperoxaemic damage at that time. Our observations confirm that even when supplemental oxygen treatment is carefully controlled episodes of hyperoxaemia are not uncommon.

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Screening for undescended testes

SIR,—While the intentions of Rao *et al* in auditing and thereby seeking ways to improve the screening for undescended testes are commendable, it would seem they have failed to grasp the significance of the two 'windows of opportunity', one for diagnosis and the other for possible effective treatment, that are available in this problem.[1]

First, the best time to examine a child for undescended testes is in the newborn period because the cremasteric reflex is absent, there is little subcutaneous fat, and the scrotum is proportionately at its largest.[2] At this time you also have a 'captive market' as, in a developed country, practically all newborns will be examined at some stage by at least one health professional. The presence of testes and their positions can be recorded and all cases of abnormality or doubt should be referred for surgical opinion as soon as possible. Efforts at improving screening will most profitably be directed at this age group rather than at a later age when physical characteristics and logistics combine to make screening less effective as was shown in their study.

Evidence exists to support the phenomenon of the apparently acquired 'ascending testis' in which a previously descended testis subsequently ascends to a truly undescended position.[3] Neonatal screening may miss this group and this may be where later screening can have a limited but useful role. Even so, there is evidence to suggest that some of these ascending testes occur in boys with incompletely descended testes at birth which subsequently descend in the first few months of postnatal life only to ascend and become undescended again at a later age.[4] These 'late descenders' could be detected at neonatal screening and referred for careful surgical supervision.

Secondly, we would agree that late orchidopexy beyond 2 years of age appears to have little or no influence on fertility or the risk of malignancy.[5] In more recent years, paediatric surgeons have been tending towards early operations before the age of 2 years but the results of this approach still remain to be seen because of the obviously long follow up required. Histological studies, however, have shown that the undescended testis appears to be normal in the first year, but by the end of the second year pathological changes are present, and progress rapidly.[6 7] Logic therefore dictates that if surgery is to have any influence on the development of the undescended testis it should be performed before the age of 2 years. This renders invalid the authors' proposal that screening be performed at the preschool age of 5 years.

It seems invidious, and certainly irrelevant, to even attempt to assess critically the performance of health visitors in a screening procedure for which they receive absolutely no training and are not even expected to perform in their routine assessments of children (LE Morgan, personal communication), as was indeed mentioned in the paper. If you are not even looking for something it should surprise no one that you do not find it. It would also not be surprising if most of the referrals from health visitors resulted from prompting by parents who had noticed a problem as over 40% of the cases in the study were self referrals by parents.

A screening programme directed primarily at 5 year old preschool children is too late. It can only serve to detect the ascending testes and the small number of undescended testes that have escaped detection in early infancy.

We would advocate examination of all neonates at birth to document testicular position. Those with an empty scrotum should be seen again at 3 and 6 months, at which time the testes of premature babies and later 'ascending testes' will be down. Those babies with an empty scrotum at 3 to 6 months can be referred for surgery at 1 to 2 years, while those with delayed descent should be followed up actively to see if the testis reascends.

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1 Rao M, Wilkinson J, Benton DC. Screening for undescended testes. *Arch Dis Child* 1991;66: 934–7.
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Drs Rao, Wilkinson, and Benton comment:

We are grateful to Dr Goh and Dr Hutson for their comments. We agree that testicular screening should start at the neonatal examination. Testicular screening in our district *does* begin with the neonatal examination—as mentioned in our article. What we discovered as a result of our audit was that a major proportion of cases of undescended testes were not detected at the neonatal stage but at the school entry examination at 5 years of age. We are therefore compelled to recommend that a 'final' screen at around 5 years is continued at present. Detection at 5 years may not be ideal but it is better than no detection at all.

A programme of systematic and uniform developmental checks for all boys under 5 years is being introduced throughout the district, in keeping with the national directive on child health surveillance.[1] If the new programme achieves the desired effect of early detection, testicular screening at school entry may become unnecessary in the future.

The purpose of our audit was to assess the effectiveness of local screening for undescended testes. To achieve this it was necessary and appropriate to examine the involvement of all the professional groups who contributed to the developmental surveillance of those aged 0–5, including health visitors. General practitioners were unaware that health visitors were not required to check testes, as indeed were two out of the three authors of this study. This fact only became generally recognised as a result of the audit.

The ineffectiveness of a programme is so often caused by problems which seem completely obvious—in retrospect. The purpose of audit is to reveal these problems, however self evident they may appear, as frequently this is the only way to motivate change in an organisation.

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Factors associated with chronic lung disease in preterm infants

SIR,—Professor Cooke's assertion that . . . 'parenteral lipid emulsions should be restricted to older preterm infants, or to those without respiratory symptoms'[1] is not warranted by the original data he presents or the published work he cites.

I do not dispute that his anlaysis demonstrates *association* between chronic lung disease and parenteral lipid therapy but correlation is a notoriously weak proof of *cause*. In this case why cannot one contend that the longer a baby is ventilated, the more likely he is to receive parenteral lipid? The conclusions of such an analysis also depend on which variables one includes or, more importantly, ignores. The vitamin A intake (lowest in the infants receiving most parenteral nutrition) could exemplify the latter category.

In support of his hypothesis, Professor Cooke cites a small randomised study[2] as demonstrating that lipid-treated infants '. . . showed a significant excess of chronic lung disease. . .', though the difference in incidence of bronchopulmonary dysplasia (BPD) between the lipid-treated and control groups was not significant by conventional criteria (lipid group 14/20, control group 10/22, $p<0{\cdot}1$). Admittedly the duration of respiratory support and supplemental oxygen treatment was greater in the lipid-treated group ($p<0{\cdot}05$), but the alveolar–arterial oxygen tension difference was somewhat greater in these infants *before* randomisation. It is true that a randomised study of *vitamin A supplementation* demonstrated a reduced incidence of both BPD and retinopathy,[3] but avoidance of lipid emulsion could only exacerbate fat soluble vitamin deficiency.

Fat is a major nutrient which provides about half the non-protein energy intake in most parenteral nutrition regimens and it could not be omitted without constraining amino acid intake too. There is a temptation to increase glucose intake to overcome this problem but this increases both oxygen consumption and carbon dioxide production, further stressing a ventilated immature baby. Lipid emulsions also supply essential fatty acids, important for growth of the nervous system and the synthesis of prostaglandins and leukotrienes. An infant of 26 weeks' gestation (1% fat by weight) would rapidly develop deficiency.

I do not dismiss the possibility that some relationship between chronic lung disease and lipid infusion exists, but would argue that randomised studies of dosage and solution composition are the way forward, not draconian proscription. Neonatal intensive care certainly is a 'continuing experiment'[1] but let us make sure it is adequately controlled.

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1 Cooke RWI. Factors associated with chronic lung disease in preterm infants. *Arch Dis Child* 1991;**66**:776–9.
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SIR,—We read with interest Professor Cooke's paper on factors associated with chronic lung disease (bronchopulmonary dysplasia, BPD) in preterm infants.[1] His retrospective study shows an association between lipid use in the first 21 days of life and the incidence of chronic lung disease. Details of lipid use are scanty—there is no information on total duration of lipid emulsion, time of start of emulsion in other than 10 day bands, whether lipid emulsion was reduced as enteral feeds were increased, how often hypercholesterolaemia or hypertriglyceridaemia occurred and if lipid emulsion was reduced accordingly, how many babies received 4 g/kg/day of lipid emulsion (20 ml/kg/day of 20% Intralipid) and so on. An association was also noted between BPD and both gestational age and septicaemia. However, association does not imply causation, and can only generate a hypothesis to be tested.

The association noted from this retrospective study should be investigated by a prospective randomised controlled study, comparing the current nutritional package in use in the Mersey unit for babies of 24 to 30 weeks' gestation with an intervention in which lipid is used only in babies of this gestational age range who have no respiratory disease. With the quoted (1988/9) rate of BPD in the unit of 60%, an intervention to reduce the rate to 40% would require a sample size of 126 babies in each group for the study to have a power of 90% and significance level of 0·05. As 40% of babies die or are breathing air by 28 days, the total sample size would need to be 420 babies. In a single centre study, this would require 10 years to complete at current rates of preterm birth in the Mersey region. If the intervention reduced the rate of BPD to 25%, a total sample size of 123 babies would be required.

Without such a study, we believe that the last paragraph of this paper is invalid. Professor Cooke recommends that parenteral lipid should be restricted to older preterm infants, or those without respiratory symptoms in the belief that the risks of an increased incidence of BPD outweigh 'theoretical gains made from early lipid infusion'. We believe that the balance of risk and benefit should be reversed, and that the harm caused by lipid deprivation may greatly outweigh any theoretical reduction in the incidence of BPD. Undernutrition is a major problem in babies who develop BPD, with late use of lipid emulsion and frequent periods of lipid-free alimentation being among the main reasons.[2] Lipid emulsion is energy rich and thus helps avoid the risk of fluid overload while achieving the desired energy goal. Moreover, essential fatty acid deficiency quickly develops in preterm babies who are deprived of lipid.[3] Fat soluble vitamins are usually supplied as an additive to parenteral lipid emulsion. There is increasing speculation that vitamin A deficiency affects the repair of injured squamous epithelium in preterm lungs, and thus contributes to the development of BPD.[4] We would welcome a multicentre study to test Professor Cooke's hypothesis that lipid emulsion use causes an increased incidence of BPD.

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1 Cooke RWI. Factors associated with chronic lung disease in preterm infants. *Arch Dis Child* 1991;**66**:776–9.
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Professor Cooke comments:

Chronic lung disease (CLD) in preterm infants results from lung damage and abnormal healing caused by a wide variety of factors. My study is aimed to discover the cause for a step change in the incidence of CLD in our unit in 1987/8. The only variable examined that satisfactorily explained such a change was the early use of parenteral lipid, introduced at this time because of concern about poor postnatal weight gain in patients with CLD. It would of course be possible to explore this variable further in more detail and it is quite possible that only some infants, probably the sickest, are adversely affected by very early lipid infusion.

Dr Williams suggests that length of ventilation could account for the association. When duration of ventilation during the first month of life is entered in the regression, it does not account for the correlation seen. This variable was not included in the final paper because, as explained, it both may cause and be caused by CLD. Vitamin A at 800 U per day was used through the period of the study either in oral or intravenous supplements. Dr Williams is somewhat selective in his quotations from the paper of Hammerman and Aramburo, in omitting to mention that 7/20 lipid-treated infants went home on oxygen compared with 0/22 of the controls.

I agree with Dr Wilson and his senior colleagues when they state that association does not necessarily imply causation, and that my cohort study can only generate a hypothesis to be tested. However, they robustly counter my proposition that the 'theoretical gains made from early lipid infusion may be outweighed by an increase in CLD' with their own small case control study showing an association between low energy intake and CLD. Surely what is sauce for the goose is good for the gander? Also the two sets of findings are not incompatible.

Dr Wilson and colleagues offer me advice on the size of randomised controlled trial which they now feel should be conducted. Trial size calculations are based on prior assumptions about the size of the effect of the intervention and the incidence of the target condition in the population. Their calculations are correct for their assumptions, although they give no reason for choosing a reduction of CLD from 60% to 40% as the effect sought. The odds ratio for lipid use in the first 21 days was 8·1 in the study reported, suggesting that a considerably smaller study may be needed. I certainly support randomised trials and further studies are currently underway.

While there is good reason to believe that better nutrition both before and after birth may make an important contribution to improved recovery from lung disease in the preterm infant, there is also good reason to believe that early use of lipid infusions may not be the best way of achieving this.

The firmness with which this was expressed in my concluding remarks is at least partly due to editorial changes, so perhaps they should share the reputation for draconian proscription!

Aetiology of malocclusion of the teeth

Sɪʀ,—In his excellent article about the aetiology of malocclusion of the teeth,[1] Professor Leighton does not mention the most common cause of malocclusion we see on this side of the Atlantic, at least in an inner city population of New York City: prolonged bottle feeding and/or pacifier use.

We see many children over the age of 1 year who already show the typical V shape of the incisors in the maxilla, as compared with the U shape of the mandible, indicating the above, or to a much lesser extent, thumbsucking. We, therefore, encourage our housestaff very strongly to promote discontinuation of bottle feeding or pacifier use after 1 year of age. The American Association of Pediatric Orthodontists is in full agreement with this.

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Professor Leighton comments:
Many surveys have shown a relationship between sucking habits and malocculsion of the teeth in the deciduous dentition, and even in the mixed dentition. However, it has been shown in a longitudinal study extending from birth to maturity (more than 17 years of age), that the effects of the sucking habit, an increased overjet and an open bite, are both resolved eventually when the habit ceases before the permanent dentition is established.[1 2] Crossbites are usually corrected spontaneously when the deciduous canines are shed. There were a few cases where a large overjet remained, but these occurred just as frequently where no sucking habit had been indulged. The use of a comforter or prolonged use of a feeding bottle might be justifiably condemned for hygienic reasons, but not because of any effect it may have on the teeth, which is transitory.

1 Leighton BC. Symposium on aspects of the dental development of the child. 2. The early development of cross-bites. *The Dental Practitioner* 1966;**17**:145–52.
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Vocal cord paralysis as a presenting sign of acute spinal muscular atrophy (SMA type 1)

Sɪʀ,—Acute diaphragmatic dysfunction can be the first sign of spinal muscular atrophy (SMA) type 1 (Werdnig-Hoffmann syndrome),[1] but early respiratory distress due to vocal cord paralysis has to our knowledge not been reported.

Case report

A girl aged 5 weeks was admitted for a progressive inspiratory stridor of recent onset. Pregnancy, birth, and the first month of life were uneventful. Tendon reflexes were brisk. Moderate axial hypotonia without limb weakness was attributed to her respiratory problem. Direct laryngoscopy showed a complete paralysis of both vocal cords in paramedian position. Lungs and diaphragm were normal on the chest radiograph. Tracheostomy was required at 6 weeks. Extensive work-up to look for a known cause of vocal cord paralysis in infancy remained negative.[2]

At 4 months, swallowing difficulties were reported. Three weeks later a massive hypotonia with severe weakness of all extremities, areflexia, and fasciculations of the tongue were found. Facial and ocular movements were spared.

Electromyography showed denervation, with fibrillation potentials in proximal and distal muscles of the left leg and pectoralis major. Sensory and motor conduction velocities were normal, with a reduced compound muscular activity amplitude. A biopsy specimen of the quadriceps showed group atrophy with increased connective and adipous tissue. No inflammatory reaction, abnormal material, or significant ultrastructural changes were found. Serum creatine kinase was normal.

The child died at 5 months. A necropsy was refused.

Clinical evolution and results of the electromyography and muscle biopsy were typical of SMA type 1, but vocal cord paralysis was a very puzzling presentation. Tracheostomy was required before the occurrence of peripheral signs of the disease. Classically, bulbar dysfunction appears late in the course of SMA type 1, respiratory failure being a consequence of progressive involvement of intercostal muscles.

Isolated vocal cord dysfunction has been described in SMA, but in a variant of the juvenile form (type 3) with distal weakness.[3] The diagnosis of SMA type 1 should be considered when the clinician is confronted by unexplained vocal cord paralysis in infants.

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1 McWilliam RC, Gardner-Medwin D, Doyle D, Stephenson JBP. Diaphragmatic paralysis due to spinal muscular atrophy. An unrecognized cause of respiratory failure in infancy. *Arch Dis Child* 1985;**60**:145–9.
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Trends in preterm survival and cerebral haemorrhage

Sɪʀ,—The observation by Cooke that the survival of preterm infants over a 10 year period improved while cerebral haemorrhage diagnosed by ultrasound showed no significant trend remarkably makes no comment on the incidence of this pathology among deaths as opposed to survivors.[1] If the author wishes to demonstrate a relationship, or the absence of a relationship, between a potentially lethal condition and the numbers of deaths (or survivors as practitioners in child health tend to view the matter) then knowing the incidence of the condition among patients who die is invaluable.

It cannot be assumed that the overall incidence of cerebral haemorrhage as shown by ultrasound during life is identical to its incidence at death. If cerebral haemorrhage is more common in patients who die its lethal potential is to some degree demonstrated. If cerebral haemorrhage is more common in survivors, a beneficial effect or association has to be considered. If the incidence is the same then one has to regard cerebral bleeding as a phenomenon which is unrelated to death or survival and which is there by chance.

Alas the author cannot resolve this matter simply by re-examining the ultrasound reports and apportioning them to deaths or survivors. This is because it would be open to the criticism, as indeed the paper as it stands is open to the criticism, that cerebral haemorrhage occurred after the last cerebral scan and was in fact the major cause of death. This criticism can only be satisfied by postmortem ultrasonography or what is far better, necropsy. The advantage of the latter is that the age and extent of the haemorrhage and its relevance to the outcome is more accurately assessed.

As a pathologist I cannot help being amused by the irony of this situation. Pathologists are always open to the criticism that knowing the incidence of a disease in patients who die does not in itself indicate the incidence in those who are alive. The argument still carries

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weight in reverse. The paediatrician who knows only the overall incidence of cerebral haemorrhage in his patients is in no position to account for why some die.

A J BARSON
Department of Pathology,
St Mary's Hospital,
Hathersage Road,
Manchester M13 0JH

1 Cooke RWI. Trends in preterm survival and incidence of cerebral haemorrhage 1980–9. *Arch Dis Child* 1991;**66**:403–7.

Professor Cooke comments:

While I agree that 'it cannot be assumed that the overall incidence of cerebral haemorrhage as shown by ultrasound during life is *identical* to its incidence at death', I doubt that it is very different. Nowadays, most preterm infants dying in intensive care units do so after several days, when most cerebral haemorrhage has already occurred. Postmortem examinations were permitted in just over half those infants dying, and correlation with antemortem ultrasound diagnosis was very good. The timing of cerebral haemorrhage by daily ultrasound scans is likely to be considerably more accurate than necropsy.

The intention of my paper was to show that improved survival during the last decade has not been matched by a reduction in cerebral haemorrhage (in both survivors and those dying), implying that the causes of mortality and cerebral morbidity were not necessarily the same. I was not trying to suggest that haemorrhage either caused death or promoted survival.

If annual haemorrhage rates are examined according to whether the infant lived or died, no significant changes are seen over the decade. The chances of surviving with cerebral haemorrhage of any grade increased significantly from 50 to 70% over the decade because of increased survival overall. The survival of infants with major haemorrhage remains unchanged at 40%.

While appreciating the value of a good perinatal pathology service, which Dr Barson naturally seeks to emphasise, I still believe that a more complete cohort for studying survival and cerebral haemorrhage rates is likely to be achieved in vivo rather than by postmortem studies.

SPRING BOOKS

Books I used while working for the MRCP

Knowledge, it has been said, peaks early in the career of a paediatrician, around the time that membership is undertaken, and is thereafter in steady decline, supplanted by the acquisition of clinical experience. How then to achieve a peak sufficiently high to ensure the clearing of the MRCP hurdle?

In preparing for the written exam I worked, more than once, through the collections of 'grey cases' by Field and Stroobant (relatively easy) and Joss and Rose (more taxing and probably more representative!) and devoured any and all of the colour atlases (Dynski-Klein, Milner and Herber, Booth and Wozniak). A few hours spent working through a collection of 'data interpretation' problems such as that compiled by Walter, Lenton, and Gabriel (Butterworths) was time well spent.

Although many of my contemporaries based their reading around the standard British paediatric text by Forfar and Arneil, I personally found the American equivalent, Nelson (Behrman and Vaughan) to be more user friendly, though the fact that it reflects American practice is a drawback. In addition, I enjoyed working from many smaller specialist texts. I liked the layout of *Heart Disease in Paediatrics* by Jordan and Scott (Butterworths) and found *Respiratory Illness in Children* (Phelan, Landau, and Olinsky; Blackwell) another text capable of keeping me interested and awake after a night on call.

As previous contributors to this section have noted, the mysteries of child development were never so well unravelled as in Illingworth's *The Development of the Infant and Young Child* (Churchill) and it was read from cover to cover. Other texts grubby with use are Roberton's *Manual of Neonatal Intensive Care* and the Department of Health's publication *Immunisation against Infectious Disease* (particularly recommended as it was free).

Time did not permit exhaustive coverage of many of the specialist texts available and so *Liver Disease in Childhood* (Mowat), *Paediatric Neurology* (Brett; Churchill), and *Practical Paediatric Gastroenterology* (Walker-Smith, Hamilton, and Walker; Butterworths) were delved into on a (sometimes highly) selective basis.

I have always tried to keep copies of good reviews of a particular topic and have found the *North American Clinics in Pediatrics* to be a prolific source of these. The latest in the series of *Recent Advances in Paediatrics* series (edited by David; Churchill) maintains the high standards set by previous authors and is useful preparation for the viva part of the clinicals. Further recommended preparation for the viva includes a review of the past year's annotations section in this journal. Streetwise candidates will also have searched recent leader articles in the *BMJ* and *Lancet*, reading those with a paediatric bent, and only those intent on resitting will have failed to research the literature on anything paediatric receiving recent media attention!

There are, of course, many more things to be read and in retrospect the task seems no less enormous. Good luck to all those attempting the leap.

IAN MECROW
Senior paediatric registrar

Life Experiences, Development and Childhood Psychopathology. Ian M Goodyer. (Pp 292; £39 hardback.) John Wiley and Sons, 1990. ISBN 0–471–91602–1.

My first thought on receiving this book was—this is what we need, something that tells us what proved effect life experiences have on children. The author attempts to tackle this large and difficult subject, and approaches it developmentally, taking into account the different effects of the same event or stress on children at various developmental stages. Deliberate effort has been made to sort out 'fact' proved by research, from assumption and gut feeling, and to tease out key factors leading to psychopathology from those which have only a secondary effect, acting via intermediary forces. Time is also taken to elucidate the protective factors which prevent many children from collapsing under a strain, and the positive benefits of stress for personal growth. For those interested in research in this field, there are numerous hints about areas where all is speculation and guesswork, which would benefit from further investigation.

The author also draws threads together from biochemistry, physiology, and psychology to help to explain both how people react differently under similar conditions and the mechanisms by which this happens. Different techniques involved in psychological research are described.

The final section of the book is probably of the most practical use to the paediatrician or child psychiatrist. This grows out of previous chapters to suggest how to investigate and treat children whose current problems may stem from past experiences. Included is some advice regarding post-traumatic stress disorder, so much in the news recently, but with particular reference to children. The book concludes with a welcome section on how insights from psychological research should guide public policy related to children and families in the future.

There are extensive references and a useful index. As a paediatrician with an interest in aspects of child guidance I found this book informative, though requiring concentration as much of the jargon was unfamiliar. In this context, the few minor misprints were irritating and distracting. However I would recommend it as an interesting book for all who work with children to dip into and particularly as a review of the state of the art and 'where to next' for those interested in research in this field.

JANET HISLOP
Senior registrar

The Special Education Handbook. Phillip Williams. (Pp 434; £55 hardback.) Open University Press, 1991. ISBN 0–335–09314–0.

Every profession has its own jargon and special education brings together teachers, therapists, doctors, psychologists, nurses, and social workers. Anyone new to the field knows what it is like to feel bamboozled by unfamiliar terminology. They, like me, will find this book invaluable.

The term 'handbook' is somewhat misleading, this is a comprehensive reference book with items as diverse as Apgar scores and Versabraille explained. Topics are presented in alphabetical order and the whole spectrum of special educational need is covered. I was impressed by the medical entries: Down's syndrome, diabetes, and fragile X syndrome are among the many conditions that are clearly and thoughtfully discussed. The emphasis is on practical information that is relevant to education, but all the important facts are included. Medical contributions are not limited to specific conditions, there is mention here of items such as distraction testing, exclusion diets, and child abuse.

As a doctor I have found this book useful as a reference for educational terms such as DATAPAC, and for providing information on the various psychological tests in use. As a newcomer to Britain I have found the synopses of the Warnock, Fish, and Swann reports and the information on relevant legislation very helpful. Entries are readable, concise, and up to date and references for further reading are supplied throughout the text. The summary of the Children Act 1989 is one of the best I have seen so far.

This book is not a textbook but it provides enough information on an enormous range of topics to justify a place in the libraries of schools, hospitals, assessment centres, community units, and anywhere involved in special education. Its great strength is that it brings together information from a variety of disciplines in a most accessible format. I am filled with admiration for the author and editors, such interdisciplinary accord is rare!

MARY McKAY
Lecturer in child health

Common Problems in Pediatric Surgery. Jay L Grosfeld. (Pp 310; £43 hardback.) Mosby Year Book, 1991. ISBN 0–8151–3949–7.

The aims of this book are clearly defined in the preface and achieved with great success and brevity. Instead of providing yet another 'comprehensive' but dry text, here are 42 clinical topics, each 'tackled' by a different North American author.

The book is written for busy surgical registrars requiring a brief essay on the relevant aetiology and pathophysiology, but authoratitive guidelines on clinical presentation and management. The authors are well chosen for their clarity of style and their depth of experience. Each chapter finishes with a short list of references. Although most of the topics do present commonly in children's units, some, like choledochal cysts and achalasia, are rarities. The chapters on inguinal hernias are excellent and important. Topics such as trauma and vascular access are included.

This book is strongly recommended for all hospital libraries and any surgeons responsible for the care of children. Although primarily for surgeons in training, experienced surgeons will find this a most useful book, particularly when preparing lectures.

DAVID P DRAKE
Consultant paediatric surgeon

The Evidence of Children: The Law and the Psychology. J R Spencer, R Flin. (Pp 362; £19·50 paperback.) Blackstone Press Ltd, 1990. ISBN 1–85431–040–2.

The issue of the evidence of children, the law, and the psychology is an alive issue currently. With proposals for changes in practice using videotapes of evidence, as recommended by Pigot, there is a major need for an authoritative text on the examination of these issues. Both authors, J R Spencer and R Flin, have played a key part in bringing these issues to professional and public attention. They have provided an equally authoritative text which gives an excellent outline of both the English and Scottish legal systems, as well as the concept of evidence, the requirement for a detailed account of the accusatorial system within which evidence occurs, and a detailed account of the rule against hearsay.

The authors then give a full account of the issues raised when videotapes are used, for example, notions about the corroboration necessary for evidence, and the role of expert assistance. They are critical of the rules of evidence, and provide a detailed review of the psychological evidence as given by child witnesses. They then describe the proposals and the ways in which children give evidence in other contexts.

Sadly, although the case has been argued by Spencer and Flin, both in this book and in many other contexts, there is still a tremendous resistance to ensuring that the evidence given by children will have the fullest opportunity to be presented in court. Unfortunately the battle to ensure that the child's voice is heard remains to be won, and although it would appear that videotapes of children's evidence may be admissible, it also appears that children may still have to be cross questioned on that account at the time of trial rather than soon after they have given their evidence initially. The battle between the child's best interests and a defendant's best interests is a difficult one to win. Although the law has not changed entirely in children's interests, the evidence is present in this book to convince some future legislature about the need to do so.

ARNON BENTOVIM
Consultant psychiatrist

Play in Childhood. By Margaret Lowenfeld. (Pp 246; £28 hardback.) Blackwell Scientific Publications, 1991. ISBN 0–901260–84–3.

What a pleasure to reread *Play in Childhood* now published in the series *Classics in Developmental Medicine*. I began anxiously wondering how relevant the book would be. It was first published in 1935 but her holistic approach and emphasis on the children themselves and practical ways to facilitate play has much to offer in the 1990s.

The book describes the observation of play and through a series of chapters describes play as bodily activity, play as repetition of experience, as demonstration of phantasy, realisation of environment, and preparation for life. There are chapters on group games, the comic element of play, and children who cannot play.

The chapter on observation of play is practical, describing ways of encouraging play with children, and the material of play. The chapter on play as preparation for life reads of a different childhood and expectations of the roles of boys and girls and reminds us of changed perceptions about gender, but other chapters are full of practical suggestions and lively records of children's conversations in play.

There are practical descriptions of the objects used and the function of her 'world' material with examples of how children use this material. The book is clearly and coherently written empowering the reader to want to use her ideas unlike many other books on play of that period that deskill the reader with a less pragmatic approach. What clearly shines through this book is Margaret Lowenfeld's capacity to put children first and hear what they had to say.

Finally as Lowenfeld emphasised the sensory experiences of play, may I thank the publishers for the thickness and texture of the pages in the book—a pleasure to touch for the adult/child.

ANN CATTANACH
Dramatherapist-play therapist

Operative Pediatric Orthopedics. Edited by S T Canale and J H Beaty. (Pp 1159; £116·50 hardback.) Mosby Year Book, 1991. ISBN 0–8016–0392–7.

New books on the techniques and details of operative orthopaedics are currently fashionable. This book, edited by Drs Canale and Beaty is, however, from a stable from which textbooks of operative orthopaedics have come for more than a generation. The Campbell Clinic has for many years been the authority to which many orthopaedic surgeons refer before operations and their *Campbell's Operative Orthopedics* remains a classic. This book considers the problems of operative orthopaedic surgery in children and is managed in the same format. Multiple authors deal with the various orthopaedic problems in children, although Dr Canale and Dr Beaty cover nine of the 19 chapters. The valuable opening chapter deals with the common orthopaedic realignment procedures used to correct rotatary and angular deformity. Although much of this chapter is conventional, the author's method of identifying the amount of correction and the size of the wedge to be removed is not only original but very useful. In considering the general aspects of children's orthopaedics the procedure has been followed as in *Campbell's Operative Orthopedics* of detailing individual procedures, their indications, and prerequisites without being severely critical of the indications and merits. The reader is not always left with the definite view of the author's management of a particular individual case. Each section of the book is well provided with references to allow the reader to research widely around the subject. Having made this criticism it must be accepted that this is a book on operative orthopaedics and space cannot be found for all aspects of diagnosis. It does have a great deal to commend it and is undoubtedly a great contribution to the enlarging literature not only for its general quality but also to the extent to which it covers all aspects of children's orthopaedics. I am sure it will be of great value to the orthopaedic resident and the practising orthopaedic surgeon for its completeness not only of its operative surgery but also its bibliography. It could act as a source of reference for medical students and interns but its detail may be beyond them. There is no doubt, however, of the value of this text which is currently concise at just over 1100 pages and one volume. Further editions may result in a multivolumed text.

ANTHONY CATTERALL
Consultant orthopaedic surgeon

Common Problems in Pediatric Urology. E Gonzales and D Roth. (Pp 485; £50 hardback.) Mosby Year Book, 1991. ISBN 0–8151–3616–1.

This book covers a broad range of paediatric urological problems, which are presented in a stimulating manner. Each chapter commences with a short case presentation and the management is subsequently discussed by a recognised expert. Most of the chapters are of a high standard, but there are a few that lack detail.

The clinical cases have been chosen well and include most of the clinical problems facing a practising full time or maximum part time paediatric urologist.

This book is attractive as it is comprehensive, relatively short, and easy to read. It is very clinically orientated and yet provides an excellent up to date overview.

P G DUFFY
Consultant paediatric urologist

Pediatric Ophthalmology. Edited by David Taylor with Eduard Avetisov, Michael Baraitser, John Brazier, *et al.* (Pp 734; £135 hardback.) Blackwell Scientific Publications, 1990. ISBN 0-86542-117-X.

For the paediatrician who needs access to only **one** book on paediatric ophthalmology, read no further, *Pediatric Ophthalmology* by David Taylor and colleagues, is **it**. For those who want to know what makes this book stand out among its competitors, read on. There are a dozen contributors, and while not detracting from their excellent individual contributions, there is no doubting the overriding influence of David Taylor—this is his book. The consequence is a text remarkable in its clarity of style and consistent approach in both chapter design and content.

Who is this book aimed at? In the preface David Taylor carefully avoids directing attention at one particular specialty, simply stating his intention to provide a useful referenced text for referral and a practical guide to clinical ophthalmology. This has been achieved as the text can easily be digested by anyone medically qualified. One of the attractions of ophthalmology is its blend of surgical and medical aspects, but the paediatrician need not fear the dominance of the former, for as mentioned in the preface surgical details are not discussed in detail and the contributors have confined themselves to principles and indications.

Pediatric Ophthalmology contains 734 pages into which are crammed 45 chapters in six sections, and 21 appendices. The major sections are: (1) epidemiology, growth and development; (2) management; (3) infections, allergic and external eye diseases; (4) systemic paediatric ophthalmology; (5) selected topics; and (6) eye movements and strabismus. These titles are self explanatory except for section 2 on management, which deals with clinical history taking and examination, refraction, ophthalmic genetics and the visually handicapped baby and the family. The 21 appendices are concise sections on problem oriented topics. These include the red eye, reduced vision, optic atrophy, headaches, peculiar visual images, the abnormal pupil appearance in infancy, the child who fails at school, etc. Each appendix starts out by defining the problem, outlining a classification, and is then followed in most instances by a flow chart. These are a feature unique to this book, and especially valuable to the clinician who does not encounter these problems frequently, and in view of the range of topics covered, few do.

With such a wide range of subjects it is not appropriate to review chapters individually. Generally the standard is very high and many chapters are quite superb, setting a gold standard against which all future texts must be gauged. Given this high level of achievement it seems churlish to identify either high or low points—there are too many of the former, and the latter are very few. The section on nystagmus is fine as far as it goes, but would have benefited from expansion; perhaps the author does not appreciate how difficult most of us, who only infrequently encounter this sign, find this topic. Nystagmus is all too easily and frequently labelled congenital or neurological, and sometimes without adequately excluding an underlying subtle ocular disorder. Electrodiagnostic tests can be a vital component of assessment.

One of the major assets of this book is the number and excellent standard of the colour photographs, and as ophthalmology is such a visual subject they are important diagnostic aids. By intention this is not a research text, but as it contains over 3500 references and provides such an excellent clinical overview of most clinical topics, it is a sensible starting point. Two minor quibbles: first, the spelling of paediatric, which is according to the preface a reflection of international market forces. Second, Marshall Parks in the forward states that nearly all specialties in medicine and surgery can be divided naturally into paediatric and geriatric portions. This is traditional and makes some practical sense with respect to paediatrics, but ignores the decades in between, and it is not a fundamentally sound approach to concepts of development and aging, the understanding a disease process, or elucidation of mechanisms. Furthermore it unnecessarily limits the scope of this book, much of which is relevant to ophthalmology of all age groups.

Pediatric Ophthalmology by David Taylor and colleagues is without doubt the best text available. Every paediatrician should have access to it, and no library is complete without it. Although not cheap at £135, this is excellent value. Every paediatric ophthalmologist I known has already bought his/her own copy. My case rests!

ALISTAIR FIELDER
Professor of ophthalmology

Hospital Care of the Recovering NICU infant. Edited by M Douglas Jones, Christine A Gleason, Susan U Lipstein. (Pp 262; £31 hardback.) Williams and Wilkins, 1991. ISBN 0-683-04476-1.

The neonatal survivor about to go home probably deserves special attention. Whether you can write a whole book on the subject is another matter. This is an attempt to do just that and this book by a team of doctors mainly from Johns Hopkins University describes how the baby develops chronic problems, how best to detect them, and what the future may hold. Its very well written with enough, not only for the acute neonatologist, but for the other doctors, physiotherapists, and community staff who could become involved in further management.

When I first scanned the book I thought it was a hotchpotch of topics all of which could be found in any standard neonatal tome but relevant to the long term survivor. I still think that chapters such as neonatal skin conditions and hypothyroidism are out of place. They were patchy and not of relevance to the theme. The second time round, reading in more detail, the main thrust came over better. The key chapters on nutrition, viral infections, chronic lung disease, anaemia, and neurodevelopmental outcome were informative and written by people with expertise. The pathophysiology of chronic problems was clearly explained without going over the heads of the wider readership at whom the book is marketed. I was left with a very favourable impression. I wouldn't put this book top of the list for the acute neonatal unit but somewhere on the shelf, there's a place for it.

J G BISSENDEN
Consultant paediatrician

Pediatric Gastroenterology and Nutrition. Edited by William F Balistreri and Jon A Vanderhoof. (Pp 400; $95 hardback.) J P Lippincott, 1990. ISBN 0-397-58326-5.

This volume is part of a series of textbooks based on a meeting of Colorado paediatricians at Aspen, and represents the outcome of their meeting. The volume itself sets out to explore some of the more recent changes and areas of interest to paediatric gastroenterologists, and therefore is not a comprehensive textbook of paediatric gastroenterology and nutrition, but rather represents the direction of the subspecialty at the current time. The chapters are all written by participants at the symposium and are written in the form of presentation.

The opening section of the book deals with the physiology of small bowel dysfunction, particularly malnutrition and the response of luminal nutrition to growth within the small intestine itself. Although there is little of practical help to the practising paediatrician within these sections, they are well laid out and give the basic understanding to some of the abnormalities of physiology encountered within malnutrition. The remaining section on small bowel pathologies undertakes chapters on coeliac disease reviewing the current developments in diagnosis, particularly antibody studies such as α-gliadin antibody and the management of the short bowel syndrome. These are, in general, very detailed and provide a useful basis for the understanding of these conditions. The difficult subject of food sensitivity is also tackled, although very little practical information can be gleaned from this and, indeed, highlights some of the controversies involved in the diagnosis of food sensitivity at the current time. There is also a very instructive section on pseudo-obstruction and oesophageal dysmotility disorders which are becoming increasingly recognised and form part of the paediatric gastroenterologists' workload. Some of the more relevant and newer developments, particularly within the realms of new drugs, are also tackled within this section in the book, concentrating on drugs such as omerprazole, cyclosporin, and misoprostol.

There are sections relating to some of the newer enteric infections, which again concentrate predominantly on the pathogenesis and are in the main research based, but do give an understanding of some of the problems associated with the newer pathogens, such as cryptosporidium and also the management of acute infantile diarrhoea. There are some practical recommendations for rehydration, although these are very locally based to the American population. Inflammatory bowel disease is also covered, although this forms rather a small section of the book and is not really very much help regarding some of the newer issues within the management of these diseases. Liver disease is represented by primary sclerosing cholangitis, which is a rare syndrome and I would have felt that some more common paediatric liver disorders would have been of more use and interest to practising gastroenterologists and paediatric gastroenterologists. Nutrition is represented in this work by cystic fibrosis and some eating disorders in adolescents such as anorexia and bulimia. The discussion of more common disorders presenting to paediatricians may have been helpful such as obesity.

In summary—this is a book produced by a group of American paediatric gastroenterologists and very much represents their own experiences and research directions. This volume makes fascinating reading and in general is well laid out and well illustrated, although the sections of histology that are presented lose something in black and white. The references, although predominently American, are also up to date and are numerous. This book provides a useful guide, particularly to practising paediatricians and paediatric gastroenterologists in the sort of areas that are becoming increasingly important within the subspecialty. It would also be of interest to those about to embark on the Membership Examination, but is not a substitute for a more basic textbook of paediatric gastroenterology.

NIGEL MEADOWS
Consultant paediatrician

The Normal Child. By Ronald S Illingworth. (Pp 464; £22·50 paperback.) Churchill Livingstone, 1991. ISBN 0–443–04455–4.

This book should be compulsory reading for anyone involved in caring for children, particularly those without children of their own. First published in 1953 and now in its 10th edition, it provides one with the benefit of Professor Illingworth's vast paediatric experience combined with sound common sense, in an eminently readable form.

The aim of the book, stated by Professor Illingworth in his preface, is to aid the recognition of 'normal' and 'normal variants' in all aspects of child health and development. He believed that a thorough knowledge of the normal is an essential basis for the knowledge of the abnormal. Discussion of pathology and other medical subjects is therefore deliberately avoided, although physiology and psychology are mentioned where appropriate.

There cannot be many paediatricians who have not at some stage of their career seen a copy of this book. Several sections have been rewritten in this edition, including those on breast feeding, sleep problems, and the chapters on prevention. There are 300 new references, and 12 colour plates appear for the first time.

The first five chapters cover all aspects of infant feeding and weaning, with plenty of practical advice and an expanded section on colic. Next comes a description of common physical variants and symptoms that concern parents. The chapters on development begin with a summary of the basic principles of development which put what follows nicely into perspective. Sketches and tables are used to good effect, and particular attention is paid to differences in the development of the preterm infant. Normal developmental variants are then discussed at length, with a section on the advanced infant.

The highlight of the book for me was the section on behaviour. All common problems are covered, with emphasis on underlying causes and aggravating factors, and plenty of advice on management. These chapters provide a fascinating insight into the mind of the egotistic, negativistic toddler. The section on 'annoying characteristics of the developing child' could be put to good use in a family planning clinic.

This edition has two new chapters. The first, on helping children to fulfil their potential, covers aspects of child care relevant particularly to parents, including play, suitable play materials, television, parental example, and ambition. The final chapter is on child health surveillance. It seeks to emphasise the wide range of topics to be covered and the need for staff who appreciate normal and normal variants. Specific subjects are also dealt with, including dental health and child abuse.

Professor Illingworth's writing is entertaining and includes some interesting historical background (did you know that Julius Caesar had neonatal teeth, or that blow fly larvae were used as a galactogogue in days gone by?) The book is full of common sense and practical advice, and should appeal to anyone concerned with children, including parents. At £22·50 it compares favourably with other standard paediatric texts, and is excellent value. Above all, it is a classic, and every paediatrician should have a copy.

MARY FEWTRELL
Paediatric registrar

Paediatrics in the Tropics. Edited by R G Hendrickse, D G D Barr, and T S Matthews. (Pp 988; £95 hardback.) Blackwell Scientific Publications, 1991. ISBN 0–632–02675–8.

Those writing a textbook on tropical paediatrics face a formidable task. Around two thirds of the world's children live in these areas and most estimates suggest that over 95% of all deaths in children occur in the tropical areas of the world. Hendrickse and his Liverpool team have assembled a remarkable team of writers to undertake this task and all those concerned with children must congratulate them on what they have achieved. They have very adequately covered the more common paediatric problems that fill the textbooks used in the industrialised world but they have emphasised the particular differences that will be found in tropical areas. They have also found space to cover the specific diseases of the tropics that develop in children.

This reviewer would like to have seen rather more emphasis on common conditions—just two pages on whooping cough and only four on measles in a book of nearly a thousand pages seems too little. Particularly, little mention is made of the new understanding of the relationship between severe measles and the size of the infecting dose. In an excellent chapter on the respiratory system no emphasis could be found on the importance of rapid respiration in the diagnosis of pneumonia at community level. The district paediatrician who looks for guidance on how to supervise the cold chain for vaccines will not get help from this book. However, the authors are to be congratulated on all they have managed to achieve and include in this volume.

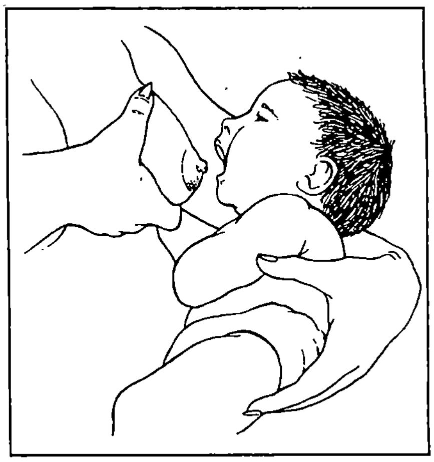
Who will get this book? It must be hoped that a volume might be available in every teaching hospital; however, the chances of this are at the present time remote. Those paediatricians with a private practice may be able to afford the £95 but few in government service could consider it, and the resources of even university libraries may not allow this book to be found on their shelves. Unfortunately, the maldistribution of resources in our world will seriously limit the enormous potential of this book to improve the health care of children in the tropics.

DAVID MORLEY
Professor emeritus

Lactation Education for Health Professionals. By R Rodriguez-Garcia, L A Schaefer, and J Yunes. (Pp 213; paperback.) Pan American Health Organisation, 1990. ISBN 92–75–12024–2. (Obtainable from Georgetown University School of Medicine, Department of Ob/Gyn, 3800 Reservoir Road, NW Washington, DC 20007, USA.)

This book arrived in the post during National Breastfeeding Week (20–27 May). First time you heard of it? This would be understandable—press treatment of breast feeding tends to be confined to images of starving Sudanese children or to jokey pieces about complaints from a library official when a mother feeds in public. National Breastfeeding Week was organised by the National Breastfeeding Initiative, which aims to combat the high attenuation of breast feeding over the first six weeks of life (the 'lost 25%'). Responsibility for this high drop off rate must be placed at the door of health professionals, whose education on lactation management is quite inadequate. This book on lactation education is therefore timely. Targetted primarily at nursing students, but readily adaptable for doctors, the book comprises a teaching module with supporting papers for the use of teachers, giving scientific background.

The product of a PAHO (Pan American Health Organisation) symposium, the text has an American flavour and a developing country orientation. The greater part of the book is taken up by a description of the module. It is very comprehensive and reveals the enormity of the gaps in medical student teaching on lactation (the whole of nutrition frequently falls between six or seven disciplines in UK medical schools). There are 15 topics within the module, from the sociocultural, technological, and political factors influencing breast feeding practices through lactation management to evaluation of breast feeding promotion activities. Each topic is broken into objectives, core content, teaching methodology, audiovisual materials, and evaluation questions. An example of the last, in 'supporting the maintenance of breastfeeding', is 'develop a list of instructions to be given to the breastfeeding mother before she leaves the hospital concerning what she should expect in the first few weeks at home . . .'. Enviably thorough, or boringly minute details? UK teachers are more laid back (almost horizontal) in their approach, and perhaps cram all their knowledge into one lecture comparing breast with cows' milk. The planned length of the module is not mentioned, and must last several months—an impracticality in UK medical schools. However, certain technical aspects not normally taught to doctors could be extracted from the book which I personally found extremely helpful. For example, how many doctors are aware of the importance of positioning technique, which holds the key to successful breastfeeding? The picture says it all:



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Teachers of child health should certainly have this book in their library.

TONY WATERSTON
Consultant paediatrician

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Patterns of metabolic adaptation for preterm and term infants in the first neonatal week

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Abstract

There have been few comprehensive accounts of the relationships between glucose and other metabolic fuels during the first postnatal week, especially in the context of modern feeding practises.

A cross sectional study was performed of 156 term infants and 62 preterm infants to establish the normal ranges and interrelationships of blood glucose and intermediary metabolites in the first postnatal week, and to compare these with those of 52 older children. Blood glucose concentrations varied more for preterm than for term infants (1·5–12·2 mmol/l *v* 1·5–6·2 mmol/l), and preterm infants had low ketone body concentrations, even at low blood glucose concentrations. Breast feeding of term infants and enteral feeding of preterm infants appeared to enhance ketogenic ability. Term infants had lower prefeed blood glucose concentrations than children but, like children, appeared to be capable of producing ketone bodies.

This study demonstrates that neonatal blood glucose concentrations should be considered in the context of availability of other metabolic fuels, and that the preterm infant has a limited ability to mobilise alternative fuels.

The newborn infant at birth must adapt from the environment in utero, characterised by the transplacental intravenous delivery of nutrients, to the postnatal situation of alternating periods of enteral milk feeding and fasting. Aspects of the process of adaptation at birth and its control have been described previously.[1 2] It may be expected that the process would be different in an infant born prematurely, because the endocrine and enzyme controls of intermediary metabolism are not fully developed in the preterm infant.[3] Disburbance of glucose homoeostasis may result when this adaptation fails or is incomplete.

Hypoglycaemia is the most common manifestation of failure of metabolic adaptation in the newborn period, and was first documented over 50 years ago.[4 5] Since then many authors have commented on the incidence, clinical manifestations, and sequelae of hypoglycaemia, although there is still substantial controversy in these areas.[6]

Preterm infants are also at risk for the development of hyperglycaemia. Most at risk are very premature infants, infants who are stressed,[7] and those receiving high rates of intravenous glucose infusion.[8] However, glucose homoeostasis cannot be divorced from the consideration of other metabolic substrates and the integrity of metabolic pathways which are necessary for the hepatic production of glucose in adequate amounts. Thus, the concentrations and interrelationships of other metabolic fuels, including the gluconeogenic substrates, lactate, pyruvate, alanine and glycerol, and the fat derived fuels, non-esterified fatty acids and ketone bodies, are important as indicators of the efficiency of counter regulatory metabolic responses during glycopenia. Furthermore, interpretation of the measurements of these substrates in sick or hypoglycaemic infants is impossible without a comprehensive knowledge of the normal ranges of concentrations and interrelationships in the neonatal period, particularly during the first seven postnatal days.

Considerable attention has been given to the adaptation to enteral feeding, and its role in the prevention of hypoglycaemia.[9–11] More recently, the value of early feeding has been recognised, particularly with respect to the adaptation of the gastrointestinal and endocrine systems to extrauterine life.[12 13]

This study examines the normal concentrations and interrelationships of metabolic fuels during the critical first few days after birth, the differences between preterm infants, term infants and older children, and the effects of feeding practices on the patterns of metabolic adaptation.

Subjects and methods

A cross sectional study was performed on 218 healthy singleton infants, less than 1 week old, born in the Newcastle upon Tyne maternity units. No mother received intravenous glucose during labour. Excluded from the study were infants with birth weights below the 10th centile, infants of diabetic mothers, and infants born by instrumental or breech delivery. Nonwhite infants were excluded because of racial differences in birthweight distribution.

One hundred and fifty six babies were of 37 weeks' gestation or more (term infants). Up to day 4, 65 born by normal vaginal delivery and 51 born by caesarean section were studied to investigate the effect of the type of delivery on metabolic adaptation. Because any differences between the two groups had disappeared by 24 hours of age (see below), and as the policy was to discharge mothers of healthy term infants born by vaginal delivery by the fourth postnatal day, 36 of the 40 infants studied at the ages of 5 and 6 days had been born by caesarean section. Term infants were demand fed by breast or bottle and none received intravenous glucose. All were nursed on postnatal maternity wards.

Sixty two babies were of 36 weeks' gestation or less (preterm infants). Only clinically stable preterm infants were studied, that is those who had not been hypoxic, acidotic, or requiring inotropic support in the 24 hours before sampling. Those requiring minimal ventilatory support were included provided they were clinically stable. Enteral feeding or intravenous fluids were started within the first four postnatal hours and the total daily fluid intake was at least 120 ml/kg for each baby. Some infants were fully enterally fed, while some received intravenous 10% glucose infusions instead of, or in addition to, enteral feeds; none received intravenous amino acid solution or lipid emulsion before or at the time of study.

For all infants, note was made of the method of feeding, the time since the last feed, and the daily intake of milk or intravenous glucose.

Blood samples were taken by heelprick, the warmed foot being sufficiently vasodilated to allow free flow without compression. Cord blood (venous) was collected at the time of the delivery for those infants who were subsequently sampled at less than 6 hours of age, before enteral feeding or intravenous fluids were started. For older infants, in order to standardise conditions during sampling, blood samples were taken immediately before a feed and no less than two hours after the previous feed. Any infant receiving more than 5 mg glucose/kg/min intravenously, had the drip rate reduced to deliver 5 mg glucose/kg/min for one hour before sampling.

Samples of 40 μl blood were collected into a microcapillary tube and then placed into a tube containing 200 μl 3% perchloric acid (PCA); and 250 μl blood were collected into a heparinised container. The samples were immediately separated and frozen, pending assay by microenzymatic methods using a Cobas fast centrifugal analyser.[14] Whole blood concentrations of glucose, gluconeogenic precursors (pyruvate, alanine, lactate, glycerol), and ketone bodies (β-hydroxybutyrate, acetoacetate), together with plasma concentrations of non-esterified fatty acid (NEFA) were thus obtained. The intra-assay coefficient of variation for each assay was as follows: alanine 4·1%, pyruvate 4·6%, glucose 3·3%, lactate 5·8%, β-hydroxybutyrate 4%, acetoacetate 8%, and NEFA 1·5%. The lower limits of detection for concentrations of glucose, β-hydroxybutyrate, and acetoacetate were 1·5, 0·01, and 0·01 mmol/l respectively.

The data obtained from the study of infants after the first postnatal day were compared with metabolic data taken from a study of 52 healthy children, aged 1 month to 10 years, who had undergone an overnight fast before elective surgery.[15]

For 11 babies, there was insufficient plasma for NEFA measurement, six of these babies were preterm and five were term, ages were as follows: <12 hours (n=1), 12–24 (n=2), 2 days (n=1), 3 days (n=4), 4 days (n=1), and 6 days (n=2).

Data were analysed using the SPSS-X package. Glucose concentrations of <1·5 mmol/l were included in parametric analysis as being equal to 1·5 mmol/l. As these values represented only 1% of the total number of glucose concentration values obtained, the results obtained were the same as if non-parametric analysis of glucose concentrations had been performed.

Pearson's correlation coefficients were used to define interrelationships between substrates, and χ^2 and *t* tests were used to compare groups of infants. Ketone body and NEFA concentrations were found to have a log normal distribution, and therefore $\log_{10}$ values for these concentrations (μmol/l) were used for statistical analysis, and the values presented in tables are geometric means. A multiple regression model was constructed to investigate the effects of feed volume, between feed interval, intravenous glucose administration rate, total energy intake, gestational age, and postnatal age on blood metabolite concentrations.

Ethical approval for the study was granted by

Table 1 Mean (SEM) concentrations of intermediary metabolites in mmol/l for healthy term infants in the first postnatal week

	No	*Glucose*	*Lactate*	*Pyruvate*	*Alanine*	*Glycerol*	*NEFA*	*Ketone bodies*
Cord								
Vaginal delivery	9	4·3 (0·1)	3·45 (0·41)	0·12 (0·01)	0·36 (0·01)	0·08 (0·01)	0·21 (0·05)	0·25 (0·01)
Caesarean section	24	3·4* (0·1)	1·60** (0·17)	0·60** (0·01)	0·29** (0·01)	0·06 (0·01)	0·10* (0·01)	0·24 (0·01)
1–12 hours								
Vaginal delivery	11	3·1 (0·3)	2·03 (0·46)	0·08 (0·02)	0·39 (0·03)	0·19 (0·02)	0·40 (0·01)	0·04 (0·01)
Caesarean section	11	3·3 (0·2)	1·79 (0·20)	0·07 (0·01)	0·29* (0·02)	0·21 (0·02)	0·37 (0·01)	0·05 (0·01)
12–24 hours								
Vaginal delivery	9	3·7 (0·2)	1·95 (0·19)	0·11 (0·01)	0·32 (0·02)	0·20 (0·02)	0·35 (0·01)	0·21 (0·02)
Caesarean section	10	3·3 (0·2)	1·85 (0·16)	0·09 (0·01)	0·25* (0·02)	0·19 (0·03)	0·33 (0·01)	0·26 (0·02)
Day 2	27	3·5 (0·2)	1·84 (0·14)	0·09 (0·01)	0·23 (0·01)	0·17 (0·01)	0·50 (0·01)	0·41 (0·01)
Day 3	27	3·4 (0·1)	1·46 (0·09)	0·07 (0·01)	0·21 (0·01)	0·16 (0·01)	0·47 (0·01)	0·43 (0·01)
Day 4	21	4·1 (0·1)	1·45 (0·16)	0·06 (0·01)	0·28 (0·02)	0·12 (0·01)	0·20 (0·01)	0·10 (0·01)
Day 5	20	4·0 (0·1)	1·32 (0·10)	0·06 (0·01)	0·29 (0·01)	0·18 (0·01)	0·19 (0·01)	0·08 (0·01)
Day 6	20	4·2 (0·2)	1·68 (0·16)	0·07 (0·01)	0·32 (0·02)	0·11 (0·01)	0·12 (0·01)	0·12 (0·01)

t test, vaginal delivery *v* caesarean section *p<0·05; **p<0·01.

the ethics committee of Newcastle Health Authority. Informed consent was obtained from parents for the inclusion of each baby in the study.

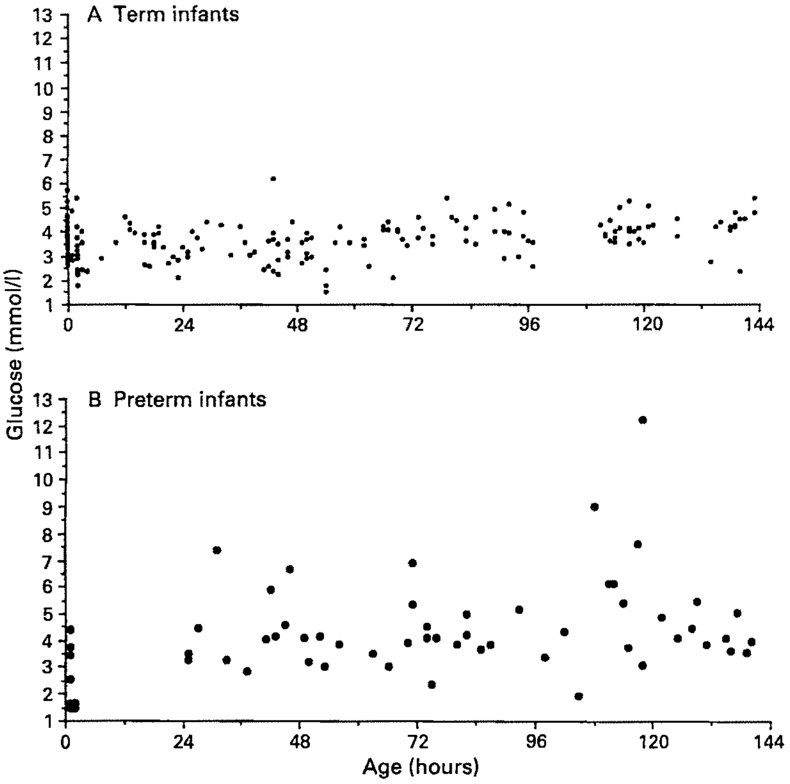

Figure 1 Relationship between blood glucose concentration and postnatal age: (A) term infants and (B) preterm infants.

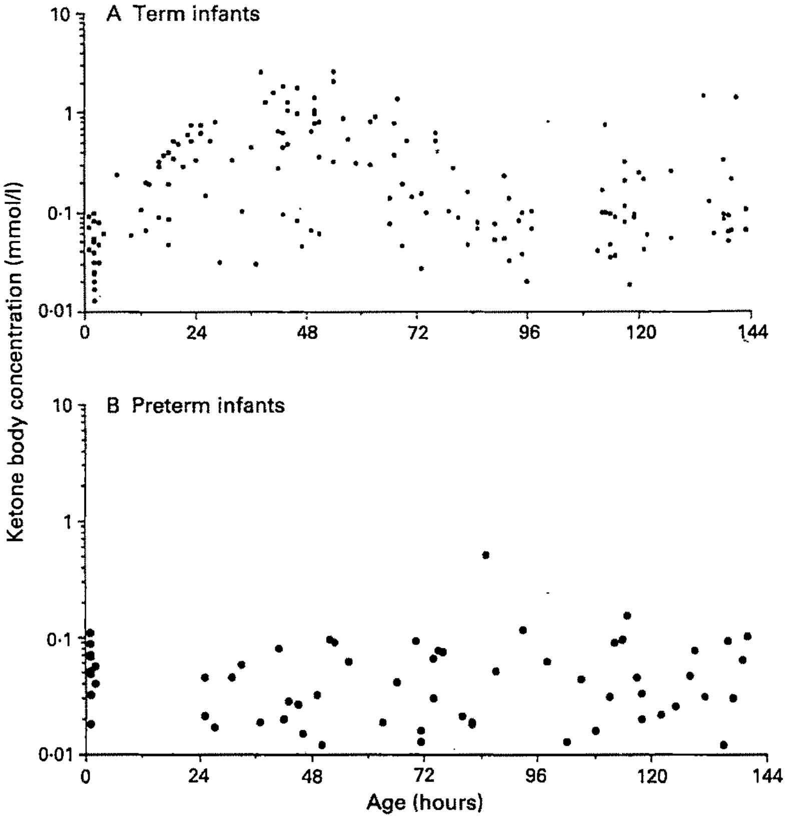

Figure 2 Relationship between ketone body concentration and postnatal age: (A) term infants and (B) preterm infants.

Results

TERM INFANTS

The median gestation of the group of term infants was 39 weeks (range 37–42 weeks), and the median birth weight was 3380 g (range 2575–4564 g). There were 83 boys and 73 girls.

The daily means (SEM) for the circulating concentrations of individual intermediary metabolites are shown in table 1. Significant differences in metabolite concentrations, between infants born by normal vaginal delivery and caesarean section, were confined to cord blood values (glucose, lactate, pyruvate, alanine, NEFA) or values on day 1 (alanine).

There were no significant differences in cord pH or between mean daily metabolite concentrations after the first postnatal day. As differences in metabolite concentrations according to mode of delivery were found only on day 1, data from infants more than 1 day old and born vaginally or by caesarean section have been analysed as one group, and babies sampled on days 5 and 6, mostly born by caesarean section, have been assumed to be representative of all babies on those days.

The range of blood glucose concentrations during the first six postnatal days was from <1·5 to 6·2 mmol/l, with the widest daily range on day 2. The lowest daily mean blood glucose concentration was found on day 1, a reflection of the low concentrations found for those infants sampled within the first six postnatal hours. Subsequently, there was a positive relationship for blood glucose concentration with postnatal age ($r=0{\cdot}41$, $p<0{\cdot}001$).

The distribution of individual blood glucose concentrations is show in fig 1A. Nineteen of 156 (12%) term infants had blood glucose concentrations below 2·6 mmol/l (the recently suggested functional definition of hypoglycaemia[16]) with all but two of these low values occurring in the first three days.

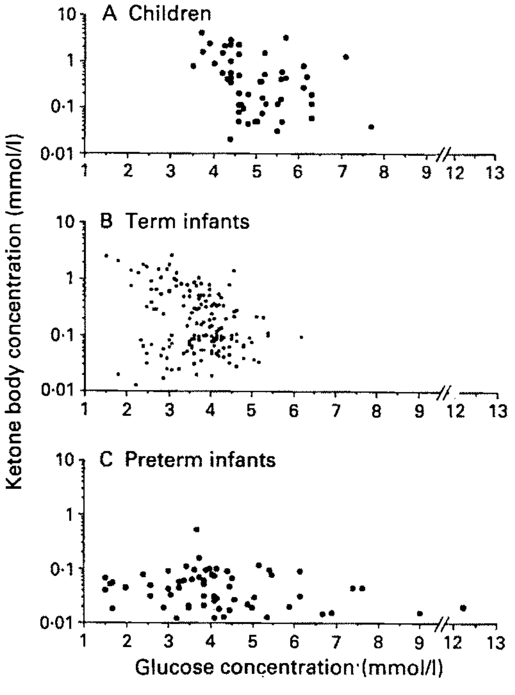

Figure 3 Relationship between blood glucose and ketone body concentrations: (A) children, (B) term infants, and (C) preterm infants.

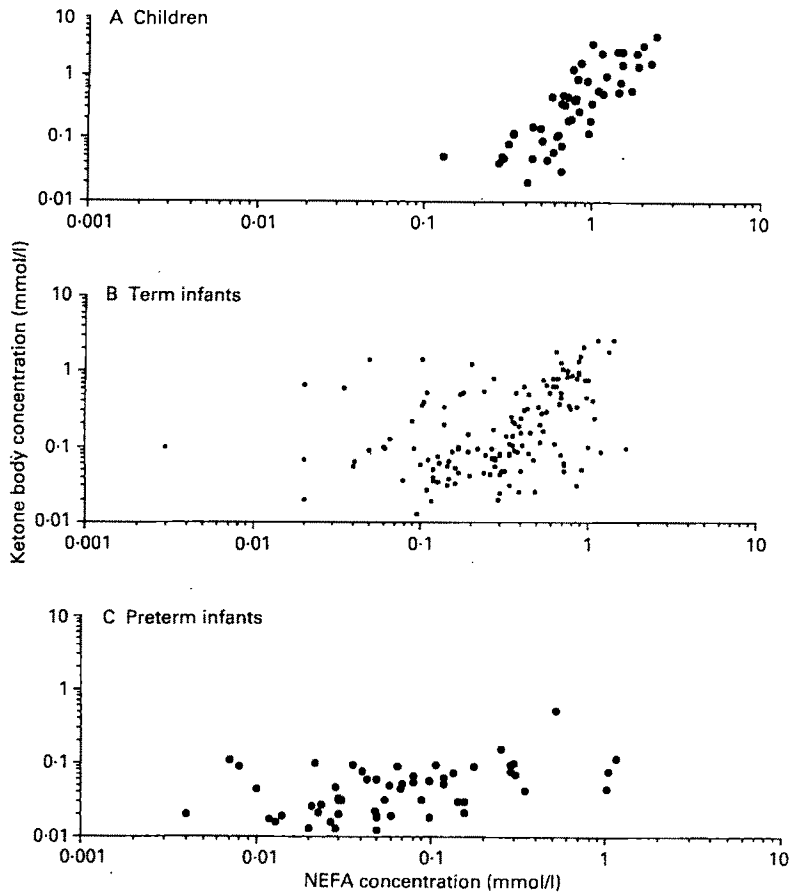

Figure 4 Relationship between ketone body and NEFA concentrations: (A) children, (B) term infants, and (C) preterm infants.

Table 2 Mean (SEM) in mmol/l for prefeed metabolite concentrations for preterm infants, term infants, and older children

	Preterm (n=52)	*Term (n=132)*	*Child (n=52)*	*t test notes**
Glucose	4·56 (0·24)	3·75 (0·07)	5·01 (0·12)	1
Lactate	1·58 (0·12)	1·60 (0·06)	1·21 (0·07)	2
Pyruvate	0·05 (0·01)	0·08 (0·01)	0·05 (0·01)	3
Alanine	0·18 (0·01)	0·26 (0·01)	0·21 (0·01)	4
Ketone bodies	0·04 (0·01)	0·20 (0·01)	0·32 (0·01)	5
NEFA	0·06 (0·01)	0·28 (0·01)	0·77 (0·01)	6
Total gluconeogenic substrate	1·90 (0·12)	2·09 (0·06)	1·66 (0·09)	7
Lactate:pyruvate ratio	32 (2)	24 (1)	26 (2)	8

**t* test notes: 1: term/preterm p<0·05; term/child p<0·001; 2: preterm/child p<0·01; term/child p<0·001; 3: term/child p<0·001; 4: term/preterm p<0·01; preterm/child p<0·01; term/child p<0·001; 5: term/preterm p<0·001; preterm/child p<0·001; 6: term/preterm p<0·001; preterm/child p<0·001; term/child p<0·001; 7: term/child p<0·001; 8: term/preterm p<0·001; preterm/child p<0·05.

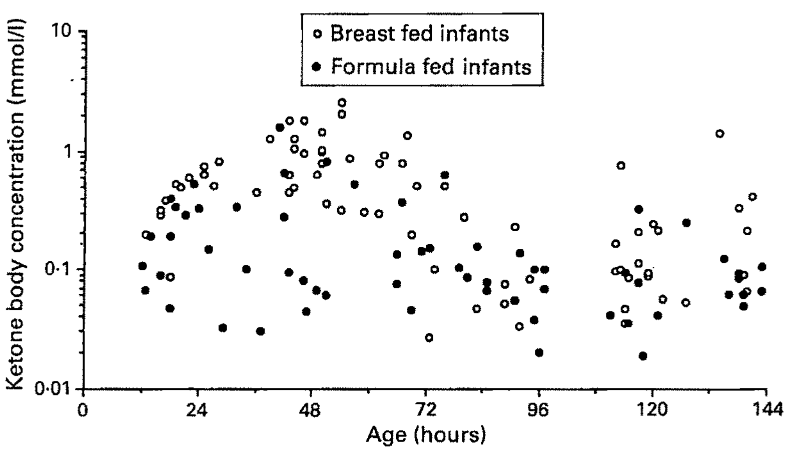

Figure 5 Relationship between blood ketone body concentration and postnatal age (term infants).

The relationship of blood ketone body concentration with postnatal age is shown in fig 2A. The highest blood ketone body concentrations were found on days 2 and 3, although the ranges of concentrations were wide on these days. On day 1 and from day 4 onwards most babies had low blood ketone body concentrations. As with older children, some term infants with low blood glucose had high ketone body concentrations (figs 3A, B). There was a significant negative relationship between log ketone body and glucose concentrations for infants aged 2–3 days (r=−0·57, p<0·001), but there was no such relationship for 1 day old infants or those older than 3 days.

The relationships between ketone body and non-esterified fatty acid concentrations for children and for term infants are shown in fig 4A, B. For term infants, Pearson's correlation coefficient for log ketone body and NEFA concentrations was 0·40 (p<0·001).

Some infants, particularly on the first postnatal day, had lactate concentrations that were above the reference ranges for older children and adults.[17] Total gluconeogenic precursor concentrations were widely scattered and were not related to blood glucose concentration. The concentrations of these substrates fell in parallel with each other in relation to increasing postnatal age (Pearson's correlation coefficient for total gluconeogenic substrate concentration with postnatal age, r=−0·24; p<0·01).

Differences between the prefeed metabolite concentrations of term infants and older children are shown in table 2. Term infants had lower mean blood glucose concentrations, but similar mean ketone body concentrations. Individual and total gluconeogenic precursor concentrations were significantly higher for term infants than for children.

Effects of feeding in term infants

Seventy one term infants were breast fed and 61 infants received formula feeds. There were no significant differences between these groups in terms of gestation, postnatal age, or distribution according to day of sampling. However, breast fed infants had significantly higher mean birth weights than formula fed infants (3507 *v* 3313 g, p<0·05) and had higher standard deviation scores for birth weight (0·67 *v* 0·28, p<0·05). Breast fed infants up to a week old had a significantly lower mean blood glucose concentration (range 1·5–5·3 mmol/l; mean 3·6 mmol/l) than formula fed infants of the same age (range 2·5–6·2 mmol/l; mean 4·0 mmol/l) (p<0·05). The distribution of blood ketone body concentrations with postnatal age, according to feed type is shown in fig 5. Breast fed infants had significantly higher blood ketone body concentrations than formula fed infants on days 2 and 3 (0·76 *v* 0·15 mmol/l, p<0·001), but after day 3 there was no significant difference in ketone body concentrations between the groups. Breast fed and formula fed infants demonstrated similar ketogenic responses to low blood glucose concentrations (fig 6).

Breast fed infants in the first postnatal week had higher total gluconeogenic substrate con-

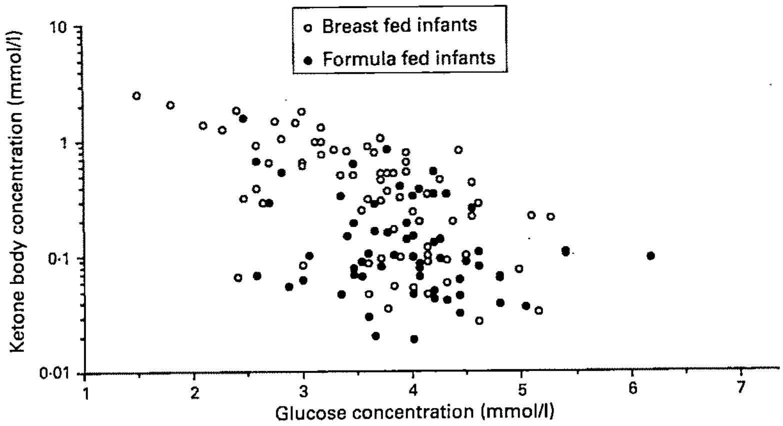

Figure 6 Relationship between blood ketone body and glucose concentrations (term infants).

centrations than formula fed infants (means, 2·2 *v* 1·9 mmol/l, $p<0·01$), but there was no difference in mean NEFA concentrations, and the method of feeding had no influence on the relationship between NEFA and ketone body concentrations.

Multiple regression analysis with method of feed, between feed interval, volume of feed, and postnatal age as independent variables demonstrated that only between feed interval (minutes) was significantly correlated with blood glucose concentration ($B=-0·003$, $SE=0·001$, $\beta=-0·32$; $p<0·05$). None of these variables, nor blood glucose concentration, could be shown to relate to total gluconeogenic substrate concentration, nor to (log) ketone body concentration when multiple regression analysis was performed either for infants 2–3 days old or for those more than 3 days old.

PRETERM INFANTS

The median gestation of the infants studied was 31 weeks (range 25–36 weeks) and median birth weight was 1760 g (range 830–3203 g). There were 40 boys and 22 girls. In terms of antenatal influences, mothers of the preterm group had a greater incidence of obstetric problems in pregnancy (for example, antepartum haemorrhage, pregnancy induced hypertension) and in labour, than mothers of the term group ($p<0·001$ and $p<0·01$, respectively), and there was a higher incidence of fetal distress in the preterm group ($p<0·05$). Despite this, the groups of infants were metabolically similar at birth, with no significant differences in umbilical venous blood pH, glucose concentration, or concentration of any other metabolite measured.

However, the preterm group subsequently had a lower mean blood glucose concentration in the first few postnatal hours than the term group (2·5 *v* 3·2 mmol/l, $p<0·05$), and a higher mean total gluconeogenic substrate concentration (4·2 *v* 2·5 mmol/l, $p<0·05$). The daily means (SEM) for the concentrations of individual intermediary metabolites are shown in table 3.

There were no significant differences between infants born by normal vaginal delivery and those born by caesarean section in terms of cord blood pH, cord blood metabolite concentrations, or blood metabolite concentrations in the first week or on each postnatal day.

The mean blood glucose concentration during the first six postnatal days was 4·2 mmol/l (range <1·5 to 12·2 mmol/l). Only on day 1 was the mean blood glucose concentration significantly lower than on subsequent days ($t=3·7$, $p<0·01$). The distribution of individual blood glucose concentrations by age is shown in fig 1B. Nine of 62 infants had blood glucose concentrations below 2·6 mmol/l, but seven of these infants were sampled on the first postnatal day before starting enteral or intravenous feeding.

The relationship of blood ketone body concentration with postnatal age is shown in fig 2B. Compared with term infants, preterm infants had low ketone body concentrations which varied little during the first postnatal week. The one infant who had a high ketone body concentration (on day 4) had a blood glucose concentration of 3·7 mmol/l.

For preterm infants, there was no significant relationship between log ketone body and glucose concentrations (fig 3C), with no rise in ketone body concentrations at low blood glucose as seen in most term infants and older children (figs 3A, B).

The relationship between ketone body and non-esterified fatty acid concentrations is shown in fig 4C. Most of the preterm infants had low NEFA concentrations, but there was a direct relationship between log ketone body and log NEFA concentrations ($r=0·46$, $p<0·001$).

Table 3 Mean (SEM) concentrations of intermediary metabolites in mmol/l for healthy preterm infants in the first postnatal week

	No	*Glucose*	*Lactate*	*Pyruvate*	*Alanine*	*Glycerol*	*NEFA*	*Ketone bodies*
Cord	11	4·2 (0·3)	2·73 (0·44)	0·10 (0·01)	0·38 (0·05)	0·07 (0·01)	0·10 (0·01)	0·16 (0·01)
Day 1	10	2·5 (0·3)	3·54 (0·76)	0·12 (0·03)	0·39 (0·07)	0·17 (0·04)	0·07 (0·01)	0·05 (0·01)
Day 2	11	4·5 (0·4)	1·49 (0·18)	0·05 (0·01)	0·19 (0·02)	0·09 (0·01)	0·05 (0·01)	0·03 (0·01)
Day 3	10	4·1 (0·4)	1·57 (0·31)	0·06 (0·01)	0·16 (0·01)	0·10 (0·01)	0·05 (0·01)	0·04 (0·01)
Day 4	10	4·1 (0·2)	1·43 (0·20)	0·05 (0·01)	0·21 (0·03)	0·09 (0·01)	0·12 (0·01)	0·06 (0·01)
Day 5	11	5·7 (0·9)	1·93 (0·38)	0·06 (0·01)	0·14 (0·02)	0·10 (0·02)	0·04 (0·01)	0·04 (0·01)
Day 6	10	4·3 (0·2)	1·46 (0·15)	0·05 (0·01)	0·20 (0·03)	0·08 (0·01)	0·10 (0·01)	0·04 (0·01)
Overall	62	4·2 (0·2)	1·90 (0·18)	0·06 (0·01)	0·22 (0·02)	0·10 (0·01)	0·07 (0·01)	0·04 (0·01)

Effects of feeding in preterm infants

The distribution of methods of feeding is shown in table 4. There were no significant differences in concentrations of glucose or other metabolites, when comparisons of groups were made according to method of feeding, although the numbers in subgroups were small. Concentrations of glucose and other intermediary metabolites were not significantly different when infants receiving any breast milk were compared with those receiving formula milk only, or when those infants receiving Pregestemil (a protein hydrolysate formula containing medium chain triglycerides, Bristol-Myers) were compared with infants receiving other types of milk formula.

Multiple regression analysis was performed with blood ketone body concentration as the dependent variable and glucose intake, total volume of feed, intravenous glucose intake, total energy intake, postnatal age, and gestational age as independent variables. Volume of feed (mk/kg/day) was found to have a significant positive correlation with log ketone body concentration ($B=0{\cdot}004$, $SE=0{\cdot}001$, $\beta=57$; $p<0{\cdot}001$), but no significant relationship was found for the other independent variables. The relationship between ketone body concentration and volume of enteral feed is shown in fig 7.

Table 4 Distribution of infants according to feeding method

	No of infants	
	Term	Preterm
Breast	71	4
Bottle	61	2
Nasogastric tube, bolus	0	14
Nasogastric tube, continuous	0	17
Combination bottle/breast/tube	0	2
Fully intravenous fed	0	8
Partial enteral/partial intravenous feed	0	15

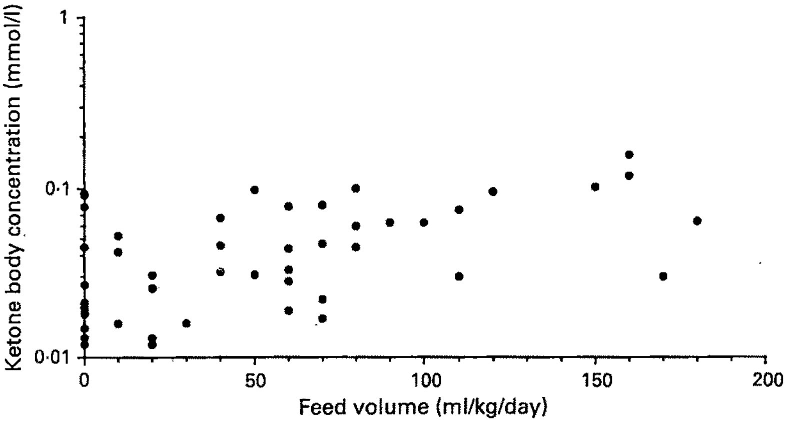

Figure 7 Relationship between blood ketone body concentration and volume of feed (preterm infants).

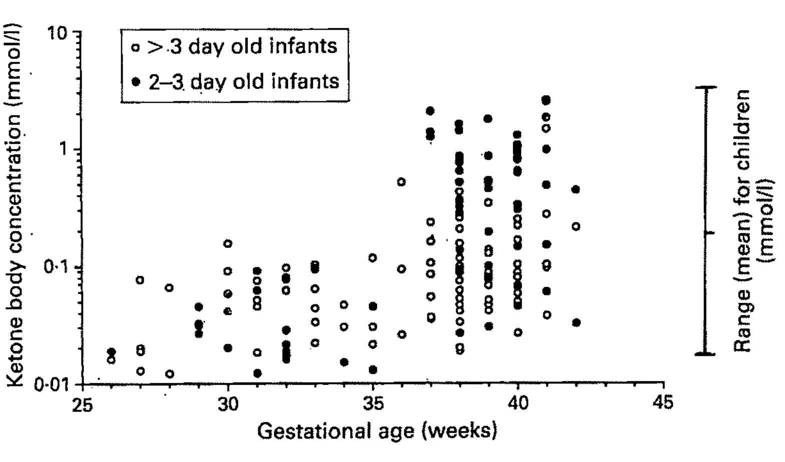

Figure 8 Relationship between ketone body concentration and gestational age.

EFFECT OF GESTATIONAL AGE

Significant differences between metabolite concentrations of preterm infants, term infants, and older children are summarised in table 2. Preterm infants had higher mean prefeed glucose concentrations than term infants, but had lower mean NEFA and ketone body concentrations than term infants and children. However, unlike term infants, gluconeogenic substrate concentrations were similar to those of older children.

On multiple regression analysis, gestational age was the most important determinant of cord blood ketone body concentration ($B=0{\cdot}03$, $SE=0{\cdot}01$, $\beta=0{\cdot}34$, $p<0{\cdot}05$), independently of size, and glucose and NEFA concentrations. Gestational age was not significantly related to cord glucose or NEFA concentrations. Once enteral or intravenous feeding was established, feed interval was the most important determinant of blood glucose concentration, there being a negative relationship between these two variables. Independently of blood glucose concentration, size or feed variables, gestational age correlated with ketone body concentration both for 2–3 day old babies ($B=0{\cdot}05$, $SE=0{\cdot}02$, $\beta=2{\cdot}6$, $p<0{\cdot}05$) and >3 day old babies ($B=0{\cdot}03$, $SE=0{\cdot}01$, $\beta=3{\cdot}4$, $p<0{\cdot}01$). Figure 8 demonstrates that an appreciable rise in ketone body concentrations occurred at 36 weeks' gestation.

Discussion

This study comprehensively describes the metabolic adaptation of a well defined group of infants, excluding any factors which may disrupt metabolic homoeostasis, with well standardised and accurate sampling and analytical techniques. Before the present study, there have been few reports of metabolic fuel profiles in the neontal period, and previous studies have been limited either by the heterogeneity of the groups studied, by studying infants over a short postnatal period, or by differences in maternal nutrition or glucose administration in labour. For example, Stanley *et al* studied only infants who were less than 8 hours old, and an earlier study of Perrson and Gentz was of subjects of mixed gestation.[18 19]

The principal findings of this study, not previously reported, are first, that vigorous ketone body production appears to be a normal part of the adaptation to extrauterine life of term babies during the first three postnatal days; second, even in mature babies, ketogenesis frequently has a different relationship to circulating concentrations of glucose and nonesterified fatty acids when compared with older children; third, that ketogenesis is severely

Table 5 Definition and incidence of hypoglycaemia

	Term				*All ages*	*Preterm*
	5 Hours		*<48 Hours*	*≥48 Hours*		
Definition (mg/dl)	<35	<30	<30	<40		<20
(mmol/l)	<1·9	<1·6	<1·6	<2·2		<1·1
Incidence (%)						
Cornblath and Reisner (1965)[20]			5	0	5	
Lubchenco and Bard (1971)[35]					7·5	
Sexson (1984)[36]		8·1				
Srinivasan *et al* (1986)[37]						
Vaginal delivery	1–2					
Caesarean section	25					
Heck and Erenberg (1987)[38]			7·9			
Chance and Bower (1966)[39]						4·3
Fluge (1974)[40]						15
Present study		0	0	3·4	3·4	3·2

limited in preterm babies. For these reasons, data from older children cannot be applied directly to the diagnosis of inborn errors of fatty acid β-oxidation. Similarly, the normal lactate: pyruvate ratio derived from older children's data may not be a reliable indicator of neonatal metabolic disorders. The profiles of metabolic fuels described in this study provide useful reference data against which disordered metabolic adaptation or inborn errors of metabolism can be considered.

HYPOGLYCAEMIA

The definition and incidence of hypoglycaemia in the newborn period have been the subjects of much controversy. Comparison of blood glucose concentrations between the present and earlier studies is hampered by the heterogeneity of infants studied previously, blood sampling and assay methods, feeding practises and intravenous administration of glucose to mothers in labour. A comparison of the incidence of hypoglycaemia between studies is shown in table 5, using early definitions of hypoglycaemia, which vary according to gestation and postnatal age of the baby.[20 21]

More recently, statistical definitions of hypoglycaemia have been challenged. It has long been suspected that neonatal hypoglycaemia has acute and long term effects on the central nervous system even at term[5 22–24] and a functional definition of hypoglycaemia has been proposed, based on neurophysiological studies and retrospective outcome analysis.[16 25] These workers suggested that the level for neonatal blood glucose concentration above which neurological dysfunction is unlikely to occur is 2·6 mmol/l.

In the present study, all umbilical venous blood glucose concentrations were above 2·6 mmol/l, suggesting adequate placental transfer of glucose before delivery. Using the functional definition, rather than Cornblath's definition, we found the incidence of hypoglycaemia for fed term infants in the first six postnatal days (10%) to be substantial, but the incidence was lower (4%) for preterm infants receiving enteral or intravenous feeds, suggesting that glucose requirements of preterm babies were being met adequately. Even when receiving enteral feeds, term and preterm infants had lower blood glucose concentrations after relatively short fasts, than had children after an overnight fast (table 2). Practical recommendations resulting from these data must take into account the ability of these babies to provide alternative fuels to glucose by metabolic counter regulation.

COUNTER REGULATION

It is likely that healthy infants may be able to tolerate low blood glucose concentrations, with compensatory mechanisms such as changes in cerebral blood flow to increase glucose delivery during hypoglycaemia,[26 27] or the use of alternative metabolic fuels such as ketone bodies, lactate or fatty acids.[28–31]

Evidence for the latter mechanism is provided by the present study, in that high ketone body concentrations were seen in term infants on days 2 and 3, with levels at this age similar to those seen after overnight fasting in older children (figs 3, 4). Turnover studies have demonstrated that there is a direct relationship between ketone body turnover rate and ketone body concentrations,[32] suggesting that the high ketone body concentrations in these babies were secondary to high rates of ketogenesis. Variation between babies may be related to the establishment of milk feeds, which may stimulate the ketogenic process, or may represent maturational differences in individual infants. Figure 3 demonstrates that, in the neonatal period, the blood glucose concentration threshold for ketogenesis is lower than for older children, and some term infants and all preterm infants with low blood glucose concentrations did not appear to mount a ketogenic response at all. The relationships between NEFA and ketone body concentrations for each group (fig 4) suggests that lipolysis and ketogenesis are less closely linked in the neonatal period especially for preterm infants, and that low ketone body concentrations in preterm babies may be related to a combined failure of lipolysis and ketogenesis. Studies of ketone body turnover would confirm these speculations.

It is interesting to note that, at birth, there appear to be few metabolic differences between term and preterm infants. This may reflect the selection of infants who all had uncomplicated deliveries and were of an appropriate birth weight for gestational age. However, in the first few hours after birth, there was a significantly greater fall in blood glucose concentration for preterm infants, suggesting that they were less able than term infants to adapt to cessation of intrauterine nutrition. The high gluconeogenic substrate concentrations for preterm infants at this age suggests that gluconeogenic ability was impaired; glucose turnover studies are required to confirm this. No mother received intravenous glucose during labour, so neonatal hyperinsulinism was unlikely to be responsible for early postnatal hypoglycaemia.

Effect of feeding

It appears that feeding affects metabolic profiles. The low glucose concentrations of breast fed term infants may reflect the low energy content of breast milk in the first few postnatal days, so that counter regulatory ketogenesis is activated.

Alternatively, the raised ketone body concentrations may be secondary to a direct ketogenic effect of breast milk, by virtue of its lipase content allowing the delivery of fatty acids to the liver via the portal venous system. Lucas *et al* studied 6 day old breast and formula fed term infants.[33] They found no differences between fasting concentration or post feed increment of glucose between the groups, although, as with the present study, ketone body concentrations were higher in breast fed infants.

For all term infants in the present study, the major determinant of blood glucose concentration was the interval between feeds, with lower blood concentrations when feed intervals were prolonged. This is in keeping with the data of Lucas *et al* who found that there were surges in blood glucose concentrations after milk feeds.[33] However, the present study demonstrates that prolonged intervals between feeds, of up to eight hours, were not associated with excessively low blood glucose concentrations. Breast fed infants, who had the lowest blood glucose concentrations, demonstrated effective counter regulation. This is reassuring in the light of current policies which encourage demand feeding of infants, and exclusivity of breast feeding when this is the mother's preference.

This study was unable to examine any differences effected by method of feeding (for example, continuous nasogastric, bolus nasogastric, bottle, breast) or type of milk on the metabolic profile of preterm infants as the groups were too small. However, after examining, by multiple regression analysis, all the factors that may affect metabolic adaptation in preterm infants, we found that there was a positive relationship between blood ketone body concentrations and the volume of enteral feed. This is the reverse of the situation found for term infants. The relationship may reflect the constituents of preterm formula feeds, but the exclusion from multiple regression analysis of infants receiving feeds containing medium chain triglycerides did not affect the findings. Alternatively, it may be that enteral feeding induces the enzymes of ketogenesis, so that metabolic adaptation, as found for term infants, can occur. This process may occur via gut hormones released in response to the presence of milk in the gastrointestinal tract, as a result of delivery of substrates other than glucose to the liver, or as a result of the carnitine content of milk enabling hepatic uptake and metabolism of fatty acids.

Much attention has been paid to the 'correct' definition of hypoglycaemia. This study demonstrates that factors other than absolute blood glucose concentration are important in the neonatal period, and while guidelines are important for clinical management, rigid definitions are inadequate and should be avoided. The influences of gestational age, feeding practises, and counter regulatory ability have also been demonstrated and these also must be considered in the interpretation of neonatal metabolic data.

We do not recommend that all asymptomatic term infants with blood glucose concentrations <2·6 mmol/l be treated with intravenous glucose, as there is evidence that, when the infants are healthy and of an appropriate weight for gestational age, ketone body production provides alternative fuels for brain metabolism. However, infants who are sick, small for gestational age, or have persistent or symptomatic hypoglycaemia, should be investigated and treated. Preterm infants appear less able to counter regulate than term infants, and hypoglycaemia should be avoided by providing adequate enteral and parenteral energy. There is evidence that enteral feeding of preterm infants is a stimulus for postnatal metabolic adaptation to occur, and this supports the view that early milk feeding to preterm infants, even at the 'minimal' level, when tolerated, should be encouraged.[12 13 34]

Future work should be directed, in all groups of infants, to blood concentration of glucose and other metabolic fuels and their relationship with neurological function, in order to identify those at most risk of neurological dysfunction at low blood glucose concentrations. Turnover studies, using stable isotopes, gas chromatography and mass spectrometry, and measurement of counter regulatory hormones will demonstrate the dynamics of endogenous glucose production and counter regulatory responses, and lead to a more scientific basis for nutritional management during the first postnatal days.

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Pulmonary and systemic arterial pressure in hyaline membrane disease

Jonathan R Skinner, Richard J Boys, Stewart Hunter, Edmund N Hey

Abstract

Systolic pulmonary arterial pressure was determined serially over the first 10 days of life in 33 babies with hyaline membrane disease by measuring the peak velocity of pansystolic tricuspid valve regurgitation, using Doppler ultrasound, and applying the Bernoulli equation. Results are presented in age groups 0–12, 13–36, 37–72, and 73–96 hours respectively. The incidence of tricuspid valve regurgitation was 92, 97, 80, and 64% (falling to 35% by day 10) compared with 53, 50, 31, and 0% in 17 healthy premature infants.

In comparing healthy babies with those with hyaline membrane disease, no allowance was made for right atrial pressure. The derived 'right ventricle to right atrial (RV-RA) pressure difference', was expressed as a ratio of systemic arterial (systolic) pressure. Over the first three days, this ratio fell much faster in the healthy babies. Values were 0·78:1, 0·77:1, and 0·72:1 in babies with hyaline membrane disease and 0·87:1, 0·53:1, and 0·44:1 in healthy babies.

Ductal patency was prolonged in babies with hyaline membrane disease (75% on day 4 compared with 6% in healthy babies). The incidence of bidirectional ductal flow, indicating balanced pulmonary and systemic arterial pressures, was 79, 53, 30, and 20%, and in healthy babies was 41% at 0–12 hours and zero thereafter.

Pulmonary arterial pressure was then calculated by adding a right atrial pressure estimate of 5 mm Hg to the RV-RA difference when the babies were ventilated. Babies of lower gestation had lower values. The pulmonary:systemic arterial pressure ratio showed considerable temporal variability, but fell with age and was raised by high mean airway pressure and pneumothorax (through a reduction in systemic pressure), and less noticeably by carbon dioxide tension. It did not correlate significantly with other indices of disease severity.

Hyaline membrane disease is associated with delayed postnatal circulatory adaptation characterised by pulmonary hypertension, systemic hypotension, and prolonged ductal patency.

The role of pulmonary vascular tone received considerable attention when the aetiology of hyaline membrane disease was first being elucidated 30 years ago. Moss *et al* were the first to demonstrate the existence of pulmonary hypertension by direct catheter measurement in 11 unventilated babies.[1] Chu *et al*, in their influential paper entitled 'neonatal pulmonary ischaemia' 25 years go, showed that pulmonary blood flow, gas transfer, and clinical status were improved by an infusion of acetylcholine, and argued that pulmonary perfusion, rather than surfactant deficiency might be the primary underlying cause of hyaline membrane disease.[2] It was only some years later that surfactant deficiency came to be accepted as the main cause.[3] Since then the part played by pulmonary vascular tone and extrapulmonary shunting has received relatively little attention, and arguably less attention than it deserves.

Due to the invasive nature of cardiac catheterisation, serial direct measurements of pulmonary arterial pressure have never been possible, but new developments in Doppler ultrasound now make it possible to estimate pulmonary arterial pressure non-invasively. The most direct technique available utilises measurement of the maximal velocity of a regurgitant jet from the tricuspid valve with application of the Bernoulli equation. This method has been validated extensively against direct catheter measurements both in adults and children.[4–8] In a previous report we showed that healthy neonates in the first three days of life commonly have tricuspid regurgitation measurable on Doppler echocardiography.[9]

The aim of the present study was to obtain serial measurements of pulmonary arterial pressure by non-invasive means in babies ventilated for hyaline membrane disease and to correlate results with the severity of the disease, blood gas status, and gestational age during the first 10 days of life.

Subjects and methods

The study group consisted of 33 ventilator dependent neonates diagnosed clinically and radiographically as having hyaline membrane disease in the two regional neonatal units in Newcastle. Babies were of 25–39 weeks' gestation (median 30·5). Birth weight was between 893 g and 3020 g (median 1651). Three babies died: at 12 hours, 9 days, and 11 days respectively. None of the babies received exogenous surfactant.

The results were compared with those obtained in the first 72 hours of life from 17 healthy premature neonates who were not ventilated, not oxygen dependent, and had no history of perinatal asphyxia. Birth weight in this group was between 1143 g and 2290 g (median 1608) and gestational age was between 28 and 35 weeks (median 32). Parental permission for serial study was obtained in all cases

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and ethical approval was granted by the district ethics committee.

MEASUREMENT TECHNIQUE

Examinations were performed by a single observer when the babies were clinically stable, starting during the first 24 hours of life, three or four times in the first five days of life, and intermittently until successful extubation. At the first examination normal cardiac anatomy was confirmed with cross sectional and pulsed Doppler echocardiography. At all examinations a detailed Doppler echocardiographic study was done using one of two Hewlett-Packard ultrasound machines. The maximal velocity of the jet of tricuspid regurgitation was measured, as previously described, using a blind 1·9 MHz probe.[9] Ductal patency was established, and flow velocities recorded, using a combination of cross sectional echocardiography, pulsed and continuous wave Doppler. Detailed clinical status was recorded and the arterial:alveolar (a:A) oxygen tension ratio was used as a measure of disease severity.[10] Systolic blood pressure was determined by indwelling arterial line or Doppler sphygmomanometry.

TRICUSPID REGURGITATION AND THE BERNOULLI EQUATION

The Bernoulli equation is derived from fluid mechanics and relates the pressure drop between two chambers to the velocity of the fluid passing between them.[11] The peak velocity of blood, measured using continuous wave Doppler, is converted into a pressure drop by application of the modified Bernoulli equation: $p=4v^2$, where p is the pressure drop (mm Hg) and v is the velocity of blood (metres/second). In the right heart, the drop in pressure from the right ventricle to the right atrium in systole can be assessed by applying the Bernoulli equation: right ventricular pressure−right atrial pressure=4×(tricuspid regurgitant jet velocity)^2.

Systolic pulmonary arterial pressure is equal to right ventricular systolic pressure if there is no pulmonary stenosis. Hence systolic pulmonary arterial pressure is equal to the drop in pressure in systole between right ventricle and right atrium plus the right atrial pressure. In the healthy neonate, shortly after birth, right atrial pressure is close to zero. Therefore in these babies no allowance for right atrial pressure is necessary.

In the babies with hyaline membrane disease, changes in right atrial pressure are still small in comparison with arterial pressure changes, but a small allowance for right atrial pressure may be appropriate to allow fair comparison of our results with previous direct measurements of pulmonary arterial pressure and with concurrent systemic blood pressure. Two of the babies in this study had single central venous pressure measurements made: one measurement was 4 mm Hg and the other 6 mm Hg. After reviewing all the available evidence,[12] we decided to allow 5 mm Hg for right atrial pressure in babies ventilated at the time of the examination when determining pulmonary arterial pressure. This allowance was made when presenting the results shown in figs 2 and 3 and tables 4 and 5. However, because this allowance can only be approximate, and to permit direct comparison between the ill and healthy babies, we have presented the actual observed pressure difference across the tricuspid valve in table 2, and called this the 'right ventricle to right atrial (RV-RA) pressure difference'.

DUCTAL FLOW

The pattern of flow during the cardiac cycle was observed and recorded along with the peak left to right flow velocity.[9 13 14] The pressure difference between the systemic and pulmonary circulations was also assessed, by estimating the pressure gradient across the arterial duct.[13 15] This was done by applying the Bernoulli equation to the maximal left to right flow velocity across the duct.

Results

INCIDENCE OF TRICUSPID REGURGITATION

The incidence of measurable tricuspid regurgitation (where the peak velocity is seen clearly) in the healthy preterm babies and the babies with hyaline membrane disease is shown in table 1. The incidence was significantly higher in babies with hyaline membrane disease throughout the first 72 hours. After this, none of the healthy babies was found to have measurable tricuspid regurgitation, and the incidence in babies with hyaline membrane disease began to fall, although it was possible to follow the course of pulmonary arterial pressure in half of the babies requiring oxygen for up to 10 days. The procedure was well tolerated by even the sickest babies as long

Table 1 Incidence of tricuspid regurgitation measurable on Doppler ultrasound in 33 babies with hyaline membrane disease and 17 healthy preterm babies

Age range (hours)	*Infants with hyaline membrane disease*				*Healthy preterm infants*		
	Mean age (hours)	*No examined*	*No ventilated*	*No (%) in whom tricuspid regurgitation measurable*	*Mean age (hours)*	*No examined*	*No (%) in whom tricuspid regurgitation measurable*
0–12	7	13	10	12 (92)*	6	15	8 (53)
13–36	23	30	26	29 (97)**	27	16	8 (50)
37–72	50	30	28	24 (80)**	44	16	5 (31)
73–96	84	25	25	16 (64)**	88	17	0
97–144	119	28	24	16 (57)			
145–192	169	17	12	7 (41)			
193–240	221	19	11	11 (58)			

Comparing babies with respiratory distress with healthy babies, *$p<0{\cdot}05$, **$p<0{\cdot}005$ by Fisher's exact test.

as they were kept warm during the examination. On some occasions measurement of the peak velocity of tricuspid regurgitation was hampered by the presence of a pneumothorax, the small amounts of interposing air being impervious to ultrasound. In one baby, with a pneumothorax on day 1, no measurements were obtainable despite some Doppler evidence of tricuspid regurgitation.

After day 6 (144 hours), fewer babies were examined because some were extubated and well. Therefore the values derived from those babies who were studied may not be descriptive of the group as a whole. If none of the babies with hyaline membrane disease who were well by 193–240 hours had measurable tricuspid regurgitation, then the true incidence of regurgitation at this time would be 35% (see table 1).

RIGHT VENTRICULAR AND SYSTEMIC ARTERIAL PRESSURES

Measurements of systemic blood pressure, and the RV-RA pressure difference are shown in table 2. Over the first 24 hours, systolic blood pressure rose by a mean of 7 mm Hg in the healthy babies. A significant rise was not seen until day 4 in the ill babies.

The RV-RA pressure difference was similar in the two groups in the first 12 hours, but then fell rapidly in the healthy babies, and more slowly in the babies with hyaline membrane disease. A comparison between the ill and healthy babies is shown in fig 1, where the RV-RA pressure difference is expressed as a ratio of systemic blood pressure.

DUCTAL FLOW

Ductal patency was prolonged in hyaline membrane disease. By day 4 all but one of the healthy premature babies had a closed duct, while in the diseased group it was still patent in 24 of 32 (75%). Only two of these 24 babies (8%) had a clinically audible ductal murmur.

Flow patterns

Bidirectional ductal flow, right to left in systole and left to right in diastole, is known to be associated with balanced pulmonary and systemic arterial pressures.[13–15] The incidence of bidirectional flow was higher in the ill babies at all ages. The difference between the groups was most noticeable at 13–36 hours when 53% of the babies with hyaline membrane disease had a patent duct with bidirectional flow, while all the healthy babies with a patent duct had pure left to right flow.

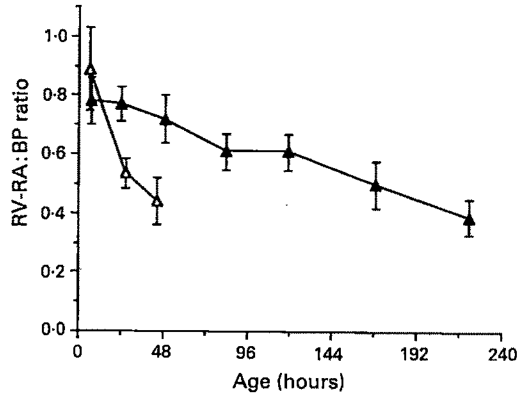

Figure 1 Right ventricle to right atrial pressure difference (RV-RA) expressed as a ratio of systemic arterial pressure (BP). Values are mean and 95% confidence limits for the mean. The closed triangles represent values from 33 babies with hyaline membrane disease and the open triangles are from 17 healthy preterm babies. (The proportion at each age who had measurable tricuspid regurgitation, allowing right ventricular pressure to be derived, are shown in table 1.)

Aorto-pulmonary pressure difference

The derived maximal pressure difference is shown for each age group in table 3. Comparing babies with hyaline membrane disease with well babies, values are similar in the first 12 hours but become strikingly different after 12 hours. This confirms the rapid fall in pulmonary arterial pressure in relation to systemic pressure in healthy babies and a slower fall in babies with hyaline membrane disease.

COMPARISON OF DUCTAL FLOW PATTERNS WITH ARTERIAL PRESSURE RATIO

The pulmonary:systemic arterial pressure ratio was compared with concurrent ductal flow patterns. There were 42 examinations with bidirectional flow and measurable tricuspid regurgitation. With no allowance for right atrial pressure the mean ratio (and its standard deviation) was 0·87 (0·17):1. Allowing 5 mm Hg for right atrial pressure in the ventilated babies the ratio was 0·97 (0·18):1. As the pressures can be expected to be approximately equal, this

Table 2 A comparison of systemic and right heart pressures in 33 babies with hyaline membrane disease and 17 healthy premature babies

Age range (hours)	*Infants with hyaline membrane disease*					*Healthy preterm infants*			
	Mean age (hours)	*RV-RA difference (mm Hg)*	*Systemic systolic BP (mm Hg)*	*RV-RA: systolic BP ratio*	*a:A ratio*	*Mean age (hours)*	*RV-RA difference (mm Hg)*	*Systemic systolic BP (mm Hg)*	*RV-RA: systolic BP ratio*
0–12	7	38·7 (9·5)†	48·8 (6·2)†	0·78:1 (0·16)†	0·19 (0·07)	6	40·3 (5·3)	49·4 (9·3)	0·87:1 (0·20)
13–36	23	35·9 (7·5)*	47·3 (6·8)**	0·77:1 (0·17)**	0·15 (0·06)	27	27·6 (2·5)	56·3 (6·4)	0·53:1 (0·07)
37–72	50	35·6 (7·6)*	49·6 (9·5)**	0·72:1 (0·18)**	0·17 (0·06)	44	25·4 (5·4)	58·8 (9·3)	0·44:1 (0·09)
73–96	84	34·6 (9·1)	56·2 (9·8)	0·61:1 (0·13)	0·29 (0·18)				
97–144	119	34·4 (6·1)	56·2 (8·7)	0·61:1 (0·13)	0·39 (0·18)				
145–192	169	32·6 (4·4)	57·2 (11·7)	0·50:1 (0·11)	0·37 (0·19)				
193–240	221	25·9 (5·4)	65·6 (10·6)	0·39:1 (0·10)	0·40 (0·24)				

Comparing babies with respiratory distress with the healthy babies: †not significant, $^{*}p<0{\cdot}01$, $^{**}p<0{\cdot}005$.
BP=blood pressure; RV-RA=maximal right ventricle to right atrial pressure difference.
The numbers examined at each age, and the proportion in whom right ventricular pressures could be derived from measurable tricuspid regurgitation, are shown in table 1. Systemic arterial pressure values are included from all babies examined, whether measurable tricuspid regurgitation was present or not.

Table 3 Ductal patency and Doppler flow characteristics from 33 babies with hyaline membrane disease and 17 healthy preterm babies

Age range (hours)	*Infants with respiratory distress*						*Healthy preterm infants*				
	Mean age (hours)	*No alive*	*No examined*	*No (%) with bidirectional flow*	*No (%) with patent duct*	*Maximum Ao/Pa pressure difference (mm Hg)*	*Mean age (hours)*	*No examined*	*No (%) with bidirectional flow*	*No (%) with patent duct*	*Maximum Ao/Pa pressure difference (mm Hg)*
0–12	7	33	13	11 (85)	33 (100)	5·9 (9·2)	6	17	7 (41)	16 (94)	9·9 (7·5)
13–36	23	32	30	16 (53)**	30 (94)**	5·6 (4·8)**	27	17	0	8 (47)	20·5 (4·1)
37–72	50	32	30	9 (30)*	28 (88)**	6·9 (6·1)**	44	17	0	3 (18)	30 (6·6)
73–96	84	32	25	5 (20)	24 (75)**	10·7 (6·9)	88	17	0	1 (6)	—
97–144	119	32	28	2 (7)	17 (53)	10·0 (7·7)					
145–192	169	32	17	1 (6)	13 (41)	16·0 (12·2)					
193–240	221	31	19	1 (5)	8 (26)	24·1 (16·4)					

Comparing distressed with the healthy babies: $^*p<0·05$, $^{**}<0·0005$.
If the arterial duct was closed at the final examination it was presumed to have remained closed.
Maximum Ao/Pa pressure difference=maximal pressure difference during the cardiac cycle between the aorta and pulmonary artery.

analysis supports the use of a 5 mm Hg constant for right atrial pressure. Therefore, for the rest of the analysis, this constant has been added when determining systolic pulmonary arterial pressure during the time period for which the babies were ventilated. The results are summarised in table 4.

FACTORS INFLUENCING PULMONARY AND SYSTEMIC ARTERIAL PRESSURE

Multiple linear regression analysis was performed to determine which factors most influenced systemic and pulmonary arterial pressures and their ratio. If a baby had more than one measurement within a single time band, one value was selected for analysis at random (this process was utilised for all the comparative analyses reported in this paper). The predictive factors tested in the analysis were: age, a:A oxygen tension ratio, inspired oxygen fraction, mean airway pressure, transcutaneous oxygen tension, and pH and carbon dioxide tension (Pco_2) from the most recent blood gas.

Pulmonary:systemic arterial pressure ratio

The regression model only explained 48% of the variability of the pulmonary:systemic arterial pressure ratio. Clearly factors other than those included in the analysis were influencing the ratio, including random variation. There was some evidence of a negative correlation with inspired oxygen fraction and a positive correlation with Pco_2. However, the most significant correlation was with age (negative) and with mean airway pressure (positive). Therefore the downward trend in the pulmonary:systemic arterial pressure ratio persisted with increasing age even with continuing severe respiratory distress. A higher mean airway pressure was associated with a higher pulmonary:systemic arterial pressure ratio. This relationship was mediated by low systemic arterial pressure and not high pulmonary arterial pressure.

Table 4 Corrected estimates of systolic pulmonary arterial pressure in babies with hyaline membrane disease. Results are mean (SD)

Age (hours)	*Systolic pulmonary arterial pressure (mm Hg)*	*Pulmonary:systemic arterial pressure ratio*
0–12	42·4 (9·2)	0·86 (0·16)
13–36	40·2 (7·1)	0·86 (0·18)
37–72	40·2 (7·3)	0·82 (0·19)
73–96	39·3 (8·9)	0·69 (0·13)
97–144	39·1 (6·2)	0·69 (0·14)
145–192	34·7 (5·2)	0·53 (0·12)
193–240	29·1 (6·1)	0·43 (0·11)

Data as in table 2, after allowing for an average right atrial pressure of 5 mm Hg in babies ventilated at the time of examination.

Systemic arterial pressure

Systemic arterial pressure correlated negatively with mean airway pressure and positively with age.

Pulmonary arterial pressure

The regression model explained less than 20% of the variability of pulmonary arterial pressure. There was a strong negative correlation with age, and a weaker correlation with Pco_2.

None of these variables correlated with the a:A oxygen tension ratio.

Utilising the serial measurements to determine the effect of disease severity, paired *t* tests were done comparing the final low value for the arterial pressure ratio with the immediate previous higher value in each baby. There was no consistent correlation with a fall in the ratio with any of the selected predictive factors.

INDIVIDUAL VARIABILITY

Serial values for the pulmonary:systemic arterial pressure ratio for the whole group are plotted in fig 2A. All the babies with hyaline membrane disease in whom three or more measurements were obtained are shown. The figure demonstrates considerable variability and a downward trend with age. In fig 2B the values derived from the healthy babies are superimposed, showing the dramatic difference between the groups despite this variability.

Examination of the serial plot (fig 2A) shows six babies with a sharp rise in the ratio at around 48 hours of age against the trend of the whole group. These are highlighted in fig 2C. Two babies, represented by the open symbols, were remarkable in having a very low ratio initially, accompanied by pure left to right ductal flow, then rising to a much higher value with bidirectional ductal flow. They were two mature babies (34 and 37 weeks' gestation) who were initially unventilated with relatively mild hyaline membrane disease. They both developed worsening respiratory distress, requiring a brief period of ventilation on days three and four. The three highest values in fig 2C were associated with systemic hypotension: two, as indicated, after a recently treated pneumothorax and the third with myocardial dysfunction secondary to myocardial ischaemia. The sixth baby was the 39 week gestation baby, who was thought clinically to have an element of persistent fetal circulation, and was receiving inotropic support. In these six cases the pulmonary:systemic arterial pressure ratio was closely related to oxygen requirements.

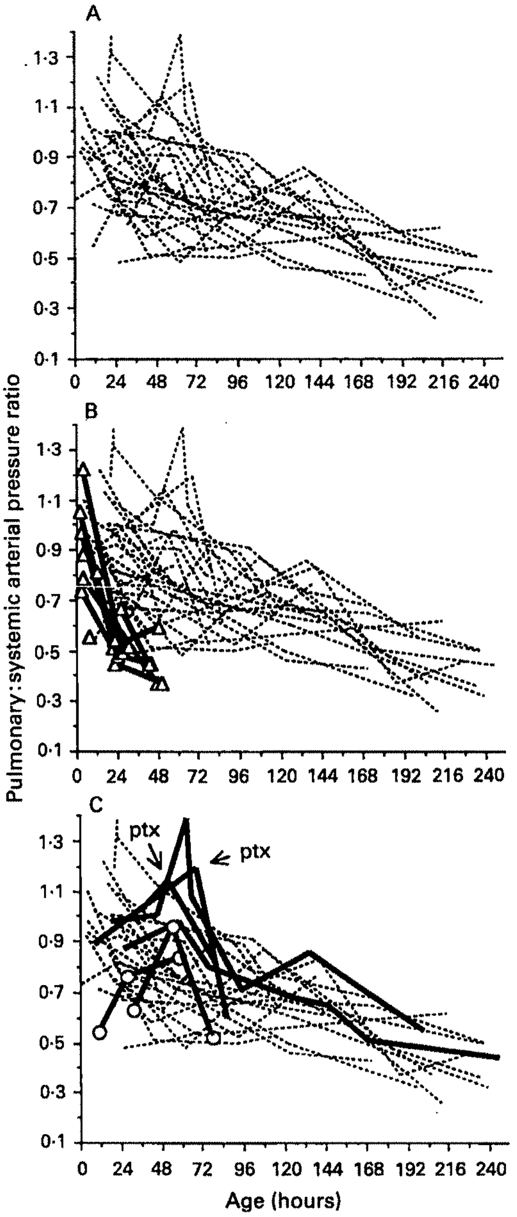

Figure 2 Serial measurements of the pulmonary:systemic arterial pressure ratio in babies with hyaline membrane disease. Systolic pulmonary arterial pressure is derived from maximal tricuspid regurgitant velocity (adding 5 mm Hg for right atrial pressure in ventilated babies). Only babies with three or more values are included. Points of measurement are excluded for clarity but are indicated by angulation changes. (A) The whole group with hyaline membrane disease. The ratios show considerable variability and a downward trend with age. (B) All the values from the healthy preterm babies (open triangles, dark lines) are superimposed on those from the babies with hyaline membrane disease. The rate of fall in the pulmonary to systemic arterial pressure ratio is much faster in the healthy babies. (C) In six babies with hyaline membrane disease, the ratio rose between the second and third day of life, against the trend (see text); ptx, recent pneumothorax.

Two other babies (of 32 and 36 weeks' gestation) were also unventilated until the third day but had high initial pulmonary arterial pressure values. In one of these babies the pressure value fell soon after ventilation was started while in the other it did not.

One baby (36 weeks' gestation, 2760 g) received tolazoline at 22 hours of age. Arterial pH was 7·34 and Pco$_2$ 6·1 kPa. Arterial oxygen saturation rose from 78% to 90%. Derived pulmonary arterial systolic pressure was 66 mm Hg and fell only marginally, to 60 mm Hg. The pulmonary:systemic arterial pressure ratio was raised (1·4:1), and is the earliest peak in fig 3A; the ratio had risen from 1·2:1 over the two hours before treatment.

After 48 hours, no babies with uncomplicated hyaline membrane disease (that is, no pneumothorax or myocardial dysfunction) had a pulmonary:systemic arterial pressure ratio over 1·0:1.

GESTATIONAL AGE

Using the arterial pressure ratio, rather than pulmonary arterial pressure alone, it was possible to compare babies of differing size and maturity directly. Babies of less than 30 weeks' gestation (mean 27·6) were compared with those of over 32 weeks' gestation (mean 35·7). The serial values are plotted in fig 3. The course over time is very varied among the larger babies, but remarkably consistent in the more premature babies. As the ratio may be transiently raised by pneumothorax, these values were excluded

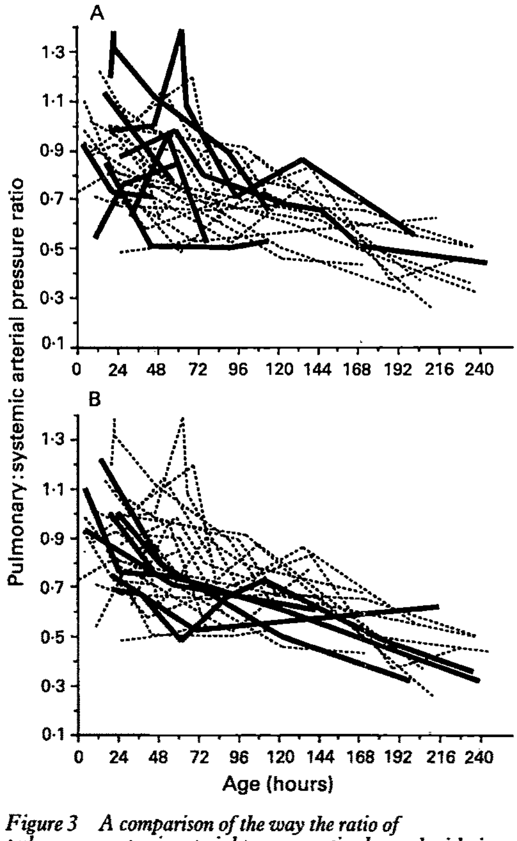

Figure 3 A comparison of the way the ratio of pulmonary:systemic arterial pressure ratio changed with time (A) in eight babies >32 weeks' gestation and (B) seven babies <30 weeks' gestation.

Table 5 A comparison of systemic and pulmonary arterial systolic pressure in infants of less than 30 weeks' gestation with infants of over 32 weeks' gestation when 13–36 hours and 37–72 hours old. Results are mean (SD)

	<30 weeks' gestation		*>32 weeks' gestation*	
	13–36 hours	*37–72 hours*	*13–36 hours*	*37–72 hours*
No of observations	11	9	8	9
Systemic arterial pressure (mm Hg)	44·8 (7·6)	51·3 (8·7)	50·3 (7·3)	53·0 (8·5)
Pulmonary arterial pressure (mm Hg)	37·0 (6·1)*	36·0 (6·4)**	44·1 (7·8)	46·6 (5·1)
Pulmonary:systemic arterial pressure ratio	0·83:1 (0·20)	0·70:1 (0·11)*	0·88:1 (0·20)	0·88:1 (0·20)
Fractional inspiratory oxygen	0·65 (0·19)	0·59 (0·19)	0·63 (0·14)	0·68 (0·19)
a:A ratio	0·15 (0·03)	0·19 (0·08)	0·18 (0·06)	0·14 (0·02)

All values are compared with more mature babies: *p<0·05, **p<0·005.

from the comparison presented here and in table 5. Pulmonary arterial pressure is significantly lower in the babies of lower gestation. The pulmonary:systemic arterial pressure ratio is initially similar, but is significantly lower in the more premature babies at 37–72 hours; this is due mostly to their larger rise in systemic arterial pressure between the two time periods.

There were no significant differences in the a:A oxygen tension ratio or inspired oxygen concentrations between the two groups. However, these are small numbers and it may be important that these figures show a trend suggesting that the more mature babies had worsening respiratory distress between the first and second age band.

Discussion

These two methods of assessing pulmonary arterial pressure are new to neonatology, so are the results reliable? It is possible to underestimate peak flow velocities if the Doppler probe is not directly in line with flow, so while overestimation is unlikely, some of the values could have underestimated the true pressure, although this was not a problem in validatory studies.[4–8] Furthermore, when ductal flow patterns were compared with the derived pulmonary:systemic arterial pressure ratio in our previous report of healthy babies over the first three days of life,[9] bidirectional flow was associated with a ratio of between 0·88:1 and 1·22:1 (mean 0·96:1), which would not suggest serious underestimation of pulmonary arterial pressure. Musewe *et al* found that, in neonates with respiratory distress, an allowance of 10 mm Hg for right atrial pressure improved the correlation of pulmonary arterial systolic pressure values obtained simultaneously from tricuspid regurgitation and from ductal flow.[15] Ten mm Hg may be appropriate in large babies with asphyxia or persistent fetal circulation, but seems too high for a preterm neonate with hyaline membrane disease.[12] This high figure may therefore represent a tendency for the tricuspid regurgitant technique to underestimate pulmonary arterial pressure in the premature neonate. This is partly supported by the observation that some babies in the present study had bidirectional ductal flow with pulmonary:systemic arterial pressure ratio below 0·8:1, even allowing 5 mm Hg for right atrial pressure. It is, however, equally possible that the ductal flow method may slightly overestimate pulmonary arterial pressure. It would seem prudent therefore to combine these two methods where this is possible and our conclusions are drawn using both of the methods. In observing trends within a subject, the allowance for right atrial pressure is less important, as this will change much less than arterial pressure.

The most striking feature in this study is the appreciable difference between the healthy preterm babies and those with respiratory distress. Pulmonary hypertension is indeed a significant part of hyaline membrane disease. This finding is consistent with those of Halliday *et al*[16] and Evans and Archer[17] who used systolic time intervals to estimate pulmonary arterial pressure in hyaline membrane disease. The present study has shown that there is a delay in the normal postnatal fall in pulmonary arterial pressure and the normal postnatal rise in systemic blood pressure. This is accompanied by persistent patency of the arterial duct. Even when the respiratory distress remains severe, the pulmonary:systemic arterial pressure ratio usually continues to fall, though at a much slower rate than in the healthy baby.

In contrast with Halliday *et al*, our study and that of Evans and Archer, found no consistent relationship with disease severity, although there was a suggestion in our study that arterial carbon dioxide tension was important and in the study of Evans and Archer that pH had an influence. Oxygen concentrations in the pulmonary artery may also have influenced pulmonary arterial pressure because oxygen is known to be a potent pulmonary vasodilator.[18 19] Oxygen saturation concentrations varied only over a fairly narrow range in most of the babies reported here, but the concentrations were almost always lower than those seen in the healthy preterm neonate.[20] It would be necessary to undertake serial studies in individual babies, while varying oxygen saturation over a wider range, to demonstrate how much influence hypoxia had on the persistent pulmonary hypertension. Such a study was done by Halliday *et al* using M mode echocardiography in babies with bronchopulmonary dysplasia.[21]

The negative influence of mean airway pressure on systemic blood pressure was independent of disease severity and is presumably related to high intrathoracic pressure impeding venous return and thereby reducing cardiac output.[22 23] The high pulmonary:systemic arterial pressure ratio is thus partly maintained by ventilation itself.

There was considerable temporal variability in both arterial pressures, and pneumothorax had a profound impact. It also appears that gestation is an important factor. Less mature babies had lower absolute pulmonary arterial pressures and a steadier fall in the pulmonary: systemic arterial pressure ratio over time. This latter feature may be a chance finding, because of the small sample size, or it could be due to a genuine difference in the disease at different gestations or to management differences. In the classical disease there is steadily worsening respiratory distress over the first two to three days, followed by steady improvement. This was seen in the four relatively mature babies who were not ventilated until they were about 48 hours old. In three of these babies pulmonary arterial pressure fell soon after ventilation, suggesting that it was higher at a time of alveolar collapse. The less mature babies were all ventilated early, and structural lung immaturity may be a further important ingredient of the disease in these babies.

A spectrum of maladaptation of the transitional circulation to extrauterine life was described by Reimenschneider *et al* who presented 13 newborn babies who were cyanosed in oxygen without structural heart disease.[24] There were three categories: pulmonary hypertension with normal myocardial function and blood pressure, pulmonary hypertension with decreased myocardial function, and systemic hypotension alone without appreciable pulmonary hypertension. The present study suggests that these circulatory disturbances can also occur without overt cyanosis and can be part of hyaline membrane disease (though they will not usually present as a clinical problem). The observation that babies can be clinically stable and acyanotic with pulmonary arterial pressure at sytemic levels and a patent duct suggests that despite pulmonary hypertension, pulmonary blood flow is adequate. This distinction is important; merely having pulmonary hypertension does not imply that it should be treated pharmacologically. Indeed, drugs such as tolazoline and prostacyclin may cause systemic hypotension,[25] already a common accompaniment of severe hyaline membrane disease,[26] and therefore cause clinical deterioration.

The present analysis has concentrated on the pressure ratios seen in systole, but pure right to left ductal shunting was never seen in any of the children in this study. Therefore it can be inferred that, during diastole (which is longer than systole), pressure in the pulmonary artery was always lower than systemic pressure, allowing a period of left to right flow with each cardiac cycle. Furthermore, it is probable that right to left shunting across the foramen ovale is at least as important in the development of persistent fetal circulation,[27] and in this context, right ventricular diastolic dysfunction may be as important as pulmonary arterial pressure. The method used by Halliday *et al* to estimate pulmonary arterial pressure is influenced by right ventricular dysfunction,[16] and this might explain why their values followed the severity of hyaline membrane disease more closely.

We conclude that there is a spectrum of postnatal circulatory adaptation among babies with hyaline membrane disease. At one extreme there are babies in whom the pulmonary: systemic arterial pressure ratio is always relatively low, even with severe disease. At the other extreme there are babies who have appreciable pulmonary hypertension, some of whom have problems related to persistent fetal circulation, even with relatively mild disease, and some of whom do not. The uniting feature of all of these babies with hyaline membrane disease is that postnatal circulatory adaptation is delayed.

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Central venous pressure in the ventilated neonate

Jonathan R Skinner, David W A Milligan, Stewart Hunter, Edmund N Hey

Abstract

As there is no other measurement of right ventricular preload, central venous pressure (CVP) measurement provides unique and important haemodynamic information. CVP is not measured routinely in neonatology and there is a shortage of data in the ventilated neonate.

CVP was measured in 62 ventilated neonates. Thirteen had respiratory disorders (28–42 weeks' gestation, birth weight 860–4390 g) and 49 had congenital heart disease (birth weight 1600–4500 g, age 0·5–30 days). Data from other case reports are also presented. In the babies with respiratory distress, a value of zero was associated with clinical evidence of hypovolaemia and negative values, common in the unventilated neonate, did not occur in those who were ventilated. Values over 7 mm Hg were found in babies with evidence of myocardial dysfunction or persistent fetal circulation but were also found with transmitted high intrathoracic pressure, such as with pneumothorax. In the babies with congenital heart disease, values mostly lay between 4 and 8 mm Hg. Values outside this range, particularly above 8 mm Hg, were usually associated with profound metabolic acidosis, suggesting circulatory failure.

While the main use of CVP measurement is in trend analysis, this report suggests that single measurements can be of value, though correct interpretation will depend on the context in which they are made.

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There has been a great deal of interest recently in the non-invasive assessment of haemodynamic function in the neonate, perhaps at the expense of invasive methods. During an evaluation of right heart pressure measurement using the Bernoulli equation,[1 2] it became apparent that there is little published data available on central venous pressure (CVP) in the sick neonate, and only limited data in the healthy neonate. This is particularly surprising as the myocardium of the sick neonate is highly dependent on an adequate preload,[3] and functions against a high afterload in the shape of pulmonary hypertension.

CVP is not monitored routinely in neonatology and there is no non-invasive measure of preload. There is a shortage of such data in the ventilated neonate, and indeed some of the reference manuals of neonatal intensive care barely mention the subject. Most available data were obtained from healthy babies, and these values (of around −2 to +4 mm Hg)[4–7] may not be relevant to the ventilated baby. In order to try to obtain 'normative reference data' for the ventilated newborn baby we have reviewed the available published data and assembled further case material from 62 neonates. Group 1 consisted of 49 babies with congenital heart disease undergoing cardiac catheterisation and group 2 of 13 babies with respiratory disease who had CVP measurements while undergoing intensive care.

Patients and methods

GROUP 1: BABIES WITH CONGENITAL HEART DISEASE

Data were available from 49 neonates with a variety of congenital heart defects who were catheterised at the regional cardiothoracic unit in Newcastle between 1977 and 1979. This represents an unselected sample from a period before the routine clinical use of cross sectional and Doppler echocardiography in neonatal cardiac diagnosis. Median age was 5 days (range 0·5–30 days); 29 (59%) were less than 8 days old. Mean weight was 3300 g (range 1600–4500).

All of the babies were ventilated and under general anaesthesia. Measurements were made using a strain gauge with either a Bentley-Trantec or a Truck transducer. Signals were transmitted via isolation amplifiers at the foot of the bed to pressure amplifiers in the main console. Recordings were made with a Siemens Elema Mingograph chart recorder and were reported by one of two consultant paediatric cardiologists.

GROUP 2: BABIES VENTILATED FOR RESPIRATORY DISEASE

Values from 13 neonates ventilated for a variety of respiratory disorders were collected between 1988 and 1991. Gestation was between 28 and 42 weeks and birth weight between 860 and 4390 g. Further details are given in the results.

Central venous access was obtained via the umbilical or the internal jugular vein. Measurements were supervised by a clinician (JRS or DWAM). A Gould P50 minidome transducer was used, connected to a Kontron Supermon pressure module.

In both groups, the catheter tip was in the right atrium and zero calibration was at the mid thorax, corresponding approximately to the level of the tricuspid valve.

Results

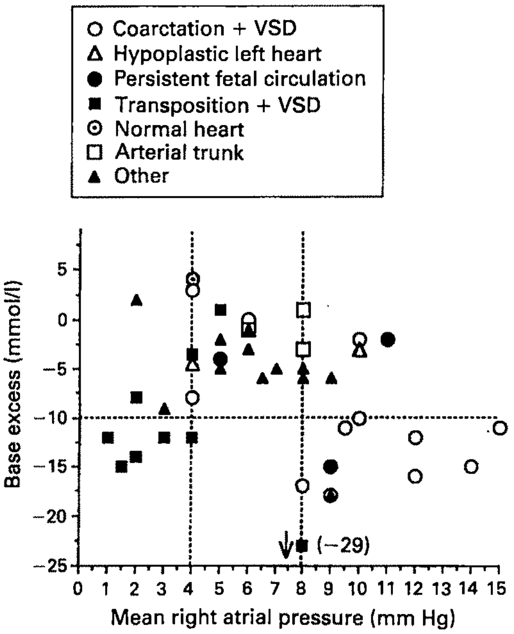
GROUP 1: BABIES WITH CONGENITAL HEART DISEASE

The results are summarised in table 1 and the

Table 1 CVP measurements (mm Hg) from 49 neonates with congenital heart disease, while ventilated and under general anaesthesia

Diagnostic category	*No of babies*	*'a' Wave*	*'v' Wave'*	*Mean*
(1) Persistent fetal circulation	3	12 (6·0)	10 (6·0)	8·3 (3·1)
(2) Obstructive left heart lesions†	15	11·3 (4·2)	10·6 (4·6)	8·9 (3·2)*
(3) Remainder	31	8·0 (3·5)	6·4 (3·6)	5·2 (2·5)*
Whole group	49	9·3 (4·3)	7·7 (4·4)	6·5 (3·2)

*p<0·001, comparing groups 2 and 3.
'a wave' represents atrial contraction, 'v wave' represents venous filling of the right atrium.
†Coarctation (n=12), aortic stenosis (n=1), and hypoplastic left heart syndrome (n=2).



Central venous pressure in 42 neonates with congenital heart disease plotted against the base excess from a concurrent arterial blood gas sample. The overlying lines highlight values between 4 and 8 mm Hg, and base excess values of −10 mmol/l or more (see text). VSD=ventricular septal defect.

figure. No values below +1 mm Hg were encountered and only five babies had values of 1 to 2 mm Hg. Of these five, three babies had an appreciable metabolic acidosis (pH <7·22, base excess >−8 mmol/l), and all three had transposition of the great arteries with ventricular septal defect. At the other extreme, there were 13 babies with a CVP of over 8 mm Hg. All but two (who had tricuspid atresia or pulmonary atresia with ventricular septal defect) were in overt cardiac failure; eight had aortic coarctation, two had persistent fetal circulation, and one had a hypoplastic left heart. Nine of these 13 babies had a severe metabolic acidosis. Twelve babies had coarctation: eight had a CVP of more than 8 mm Hg and seven of these were profoundly acidotic (as was the only baby with a CVP of 8 mm Hg) indicating circulatory failure. The other three babies with coarctation had CVP values of 4–6 mm Hg and were not acidotic. There were 22 babies with a CVP of 4–8 mm Hg and available blood gas results and only three were significantly acidotic (two had CVP values of 8 mm Hg and the other of 4 mm Hg).

GROUP 2: BABIES VENTILATED FOR RESPIRATORY DISEASE

The results are summarised in table 2, though this presentation does not demonstrate the most useful feature of CVP measurement, which comes from serial measurement. However, on all occasions when the CVP was zero, there was clinical evidence of hypovolaemia. In general, higher values were seen in the larger babies, but this observation could be explained by the nature of their illness, rather than size *per se*, with a preponderance of asphyxia and myocardial ischaemia. Low values, from 0–3 mm Hg were particularly badly tolerated in this group. The four babies with uncomplicated hyaline membrane disease who survived had CVP values within a relatively narrow band when clinically stable (2–6 mm Hg most of the time).

Table 2 CVP in 13 ventilated neonates with respiratory distress

Gestation (weeks)	*Birth weight (g)*	*Diagnosis*	*Outcome*	*Observations*		*CVP (mm Hg)*	
				No	*Age (hours)*	*Range*	*Mean*
28	1120	HMD, PPHT, PIE, ICH	Died 41 hours	21	18–39	4–9	7·0
28	1160	HMD, PPHT, PTX, ICH	Died 36 hours	4	4–8	3–5	4·0
31	1970	HMD	Alive, well	1	5	—	4·0
31	1600	HMD	Alive, well	18	13–48	0–5*	2·8
31	1945	HMD	Alive, well	22	18–40	0–6†	2·6
32	860	IUGR, asphyxia, ICH	Died 14 days	31	20–54	0–10‡	5·7
34	2540	HMD, asphyxia	Alive, well	1	82	—	6·0
36	3150	PPHT, myocardial ischaemia	Alive, well	1	48	—	9·0
38	3610	Asphyxia, myocardial ischaemia NEC	Alive, well	2	0–1	0–3§	1·5
				24	25–48	6–11	6·8
				24	49–72	5–9	6·8
				13	73–85	3–7	5·7
40	4230	Asphyxia	Died 24 hours	9	10–18	4–10	6·8
40	3210	PPHT, septicaemia	Alive, well	44	96–130	6–12	7·8
40	3335	Asphyxia, pulmonary haemorrhage, renal failure	Died 6 days	63	67–139	0–8¶	3·8
42	4390	PPHT, meconium aspiration	Alive, well	26	47–73	2–9	5·0

HMD=hyaline membrane disease, ICH=large intracranial haemorrhage, IUGR=intrauterine growth retardation, NEC=necrotising enterocolitis, PIE=pulmonary interstitial emphysema, PPHT=persistent pulmonary hypertension, PTX=pneumothorax.
*One record of zero CVP coincided with circulatory collapse and hypotension at the time of an intracerebral bleed.
†Three recordings at zero with poor peripheral perfusion and mild metabolic acidosis; 20 ml/kg of colloid caused the CVP to rise to 6 mm Hg with clinical improvement.
‡Two recordings at zero with clinical evidence of hypovolaemia.
§Umbilical line used for resuscitation with 30 ml/kg of colloid. Systolic blood pressure of 30 mm Hg rose to 45 mm Hg; CVP rose from zero to 3 mm Hg. Later values from jugular line for intravenous feeding when clinically stable on inotropic support.
¶Three episodes of hypotension/circulatory collapse, all with pulmonary haemorrhage; CVP fell to zero or 1 from 3–4 mm Hg twice, but with the preterminal event CVP rose to 8 mm Hg, with clinical and echocardiographic evidence of severe right ventricular failure.

REVIEW OF THE LITERATURE

Preterm babies with hyaline membrane disease

Rudolph *et al* recorded CVP in six babies with hyaline membrane disease; values ranged between −6·5 mm Hg and zero.[5] In such early studies of hyaline membrane disease the babies were usually unventilated and generating large negative intrathoracic pressures. Because of this influence of intrathoracic pressure, Stahlman *et al* did not report mean CVP in their studies.[8] Siassi *et al* reported a mean CVP of +1·6 mm Hg in healthy preterm neonates and negative values in 12 babies with respiratory distress with values varying from −16 to +3 mm Hg.[9] Six of these 12 babies were ventilated and they were reported to have higher values within this range. Cabal and Hodgman reported that a ventilated premature neonate developed a mean CVP of 12 mm Hg with a tension pneumothrax, which returned to 6 mm Hg after successful drainage.[10]

Todres *et al* performed Swan-Ganz catheterisation in 11 ventilated preterm neonates.[11] In two of these babies CVP was reported; both had hyaline membrane disease and septicaemia. One baby had a CVP of 2 mm Hg and the other a CVP of 0–2 mm Hg. The latter baby was clinically hypovolaemic when right atrial pressure was zero. In another study by Cabal *et al* four asphyxiated, ventilated, preterm neonates of 30–34 weeks' gestation with respiratory distress and heart failure were managed successfully with inotropes.[12] Mean CVP was 12 mm Hg at 1 hour of age (before treatment), 6·2 mm Hg at 6 hours, 5 mm Hg at 12 hours, and 4 mm Hg at 24 hours.

Term babies with persistent pulmonary hypertension

Peckham and Fox catheterised 10 ventilated babies with persistent fetal circulation and found a mean CVP of 6·6 mm Hg.[13] Tamura and Kawano investigated the clinical efficacy of nitroglycerine in the management of heart failure and persistent pulmonary hypertension.[14] Six babies had CVP recordings, two were of 32 weeks' gestation and the rest were at term; all were ventilated. The initial mean (SD) CVP was 13·8 (6·7) mm Hg falling to 10·8 (4·4) mm Hg with clinical improvement. However, this was a mixed group of babies: one had Ebstein's anomaly, one had hypertrophic cardiomyopathy, and two had diaphragmatic hernias.

Older babies with congenital heart disease

Burnell catheterised 131 infants under 1 year of age with congenital heart disease.[15] Those in heart failure had a mean right atrial pressure of 7·7 mm Hg compared with 3·5 mm Hg in those without heart failure. Some of the babies were ventilated and some were not.

Discussion

There is strong experimental evidence that the cardiovascular system in the human neonate is much less able to cope with hypervolaemic and hypovolaemic conditions than the adult.[16] Hypovolaemic shock, probably an important factor in the development of respiratory distress,[17 18] is common after perinatal asphyxia or preterm delivery. Early cord clamping can deprive the baby of over 40% of its circulating volume.[19] Hypotension is known to be associated with an increased risk of intraventricular haemorrhage,[20] and an early increase in preload by colloid administration may reduce the risk.[21] In the assessment of all these dramatic haemodynamic changes and interventions it is remarkable how infrequently CVP is measured.

It is clearly difficult to establish 'normal' values for central venous pressure as the optimal filling pressure for any individual is unique and varies with changes in ventricular performance, compliance, and afterload. However, this review would suggest that at least some guidelines can be drawn up and that although the main use of CVP measurement is in trend analysis and in monitoring treatment, some interpretation of initial or isolated measurements can be made. It appears that in the ventilated neonate, a CVP of zero is likely to be associated with hypovolaemia and inadequate right ventricular preload. In term babies with heart failure and pulmonary hypertension higher pressures are found, so a value of 3 mm Hg in this situation may also indicate inadequate preload. While values of 2–6 mm Hg are 'normal' in clinically stable preterm babies requiring ventilation for hyaline membrane disease, such values may indicate inadequate preload in the bigger baby with pulmonary hypertension. A comparison can be drawn from cardiac intensive care where right atrial pressures of up to 20 mm Hg are needed in the infant after right ventriculotomy to correct Fallot's tetralogy, and values within the 'normal range' are associated with inadequate pulmonary blood flow. The failing right ventricle requires an increased preload to maintain output as with decreased contractility a higher end diastolic volume is required to maintain stroke volume.[22] Values over 20 mm Hg are avoided because of the risk of ascites.[23]

CVP values over 7 mm Hg usually indicate myocardial dysfunction and/or pulmonary hypertension, but high values need to be interpreted with caution. The measured value may be artificially high due to raised intrathoracic pressure, secondary to pneumothorax or overventilation of compliant lungs. This may be an important factor when therapeutic alkalosis is induced by hyperventilation. The measured value may also be misleadingly low if there is coincident hypovolaemia. It needs to be remembered that CVP is related, not only to the volume of intravascular blood within the venous system and the function of the cardiac pump, but also to intrathoracic pressure.[3 9 24 25] A more ideal measure, that of central venous filling pressure, could in theory be obtained by subtracting intrathoracic pressure, measured by oesophageal manometry, from CVP but this does not seem to have been attempted in clinical practice as yet.

Todres *et al* showed that left ventricular filling pressure measured by Swan-Ganz catheterisation is a practical and useful method to assess left ventricular function in the neonate.[11] However, in the newborn there is usually biventricular failure so that CVP measurement can still be of use in babies presenting primarily with left ventricular dysfunction. This was demonstrated by the patients with aortic coarctation in our study: babies with circulatory failure, manifesting as a metabolic acidosis, had higher CVP values (over 7 mm Hg) than those who did not.

Measurement of CVP is not difficult, but it is an invasive procedure which carries potential risks. Is it likely that a non-invasive tool will be able to replace it? At present this seems unlikely. Doppler echocardiography can estimate pulmonary arterial pressure[1 26 27] and pulmonary flow by monitoring left or right ventricular output. But if pulmonary blood flow falls, what has caused the fall? We can estimate afterload, but is the preload too low or too high? This question is only answered by serial measurement of CVP. An accurate non-invasive measure of blood volume is also still awaited, though an interesting area is the measurement of the circulating peptides atrial natriuretic peptide and arginine vasopressin. Their relationship to circulating volume and atrial distension is still under research.[28 29] However, it seems likely that they will be influenced by a number of variables associated with postnatal adaptation, stress, and ventilation.

CVP values provide unique haemodynamic information, which is of particular importance to the very sick neonate. The principal use of CVP measurement is in trend analysis, but interpretation of initial or isolated measurements in the ventilated neonate assumes special importance during an episode of cardiorespiratory collapse. This review shows that single measurements can be of value, but that correct interpretation of the result will depend on the context in which it is made.

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Phosphatidylcholine composition of endotracheal tube aspirates of neonates and subsequent respiratory disease

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Abstract
The phosphatidylcholine (PC) content of the initial endotracheal tube aspirate was measured in 105 infants intubated for resuscitation or for ventilation for respiratory distress syndrome, using high performance liquid chromatography and postcolumn fluorescence derivitisation with diphenyl-1,3,5-hexatriene. Sixty eight had measurable PC. Of the infants who developed respiratory distress syndrome, with or without subsequent chronic lung disease, neither the percentage of dipalmitoylphosphatidylcholine (DPPC) nor the ratio of DPPC to palmitoyloleoylphosphatidylcholine (POPC), showed any correlation with gestational age. However, both parameters were significantly lower overall in this group than in the group of infants who did not develop respiratory distress syndrome. Infants with a ratio of DPPC:POPC <3·0 developed respiratory distress syndrome irrespective of gestational age, but there was considerable overlap between groups for values greater than this.

The infants with respiratory distress syndrome who went on to develop chronic lung disease had the same initial PC profile as those with respiratory distress syndrome who did not develop chronic lung disease, but differed as a group by being lighter and more premature. The development of chronic lung disease was not associated with a particular initial PC composition. Other factors related to increasing prematurity must therefore be involved in rendering infants vulnerable to developing chronic lung disease.

Despite the introduction of surfactant replacement treatment, respiratory distress syndrome remains one of the major causes of morbidity and mortality in premature infants, and one of its sequelae, chronic lung disease, continues to cause respiratory problems through into infancy. A biochemical parameter that accurately predicts the development of respiratory distress syndrome would enable targeting of 'prophylactic' surfactant replacement treatment, with consequent financial implications. Further, early identification of infants who are at risk for developing chronic lung disease could enable timely intervention, such as diuretic or dexamethasone treatment, in an attempt to alter outcome.

The major cause of respiratory distress syndrome is a deficiency in both quantity and quality of pulmonary surfactant. This substance is composed of phosphatidylcholine (PC) species, other phospholipids, and surfactant proteins. It has been shown that changes in the PC composition occur with increasing maturity.[1 2] In human postmortem studies an increase in disaturated PC has been demonstrated with increasing gestation.[2] Attempts to establish a reliable assessment of surfactant status have included quantitation of the disaturated PC species dipalmitoylphosphatidylcholine (DPPC), as this particular species is the most surface active component of pulmonary surfactant. However, such attempts have been restricted largely to the analysis of total disaturated PC.[2] It has been demonstrated recently that lung fluid at term contains significant quantities of another disaturated PC species myristoylpalmitoylphosphatidylcholine,[3] which is not surface active, emphasising the limitation of total disaturated PC as an index of surfactant maturity.

A sensitive method for the analysis of individual PC species has been described,[4] and employed in the study of a guinea pig model.[3 5] In this model DPPC, specifically, has been shown to increase with gestation, and palmitoyloleoylphosphatidylcholine (POPC), an unsaturated species, to decrease. Amniotic fluid and nasopharyngeal aspirates of term infants were shown to have a higher percentage of DPPC and a lower percentage of POPC when compared with amniotic fluid taken at 20 weeks' gestation.[5] The ratio of DPPC to POPC may be an index of surfactant maturity,[3 5] and has been proposed as possibly predictive for the development of respiratory distress syndrome.[5]

Currently available methods for the analysis of surfactant maturity, including the one described here, take too long to perform to be of use in predicting postnatally which babies might benefit from the use of 'prophylactic' surfactant treatment—the diagnosis of respiratory distress syndrome would be obvious clinically before the results were available. However, initial endotracheal tube aspirates are easily obtained and can form the basis for feasibility studies into any biochemical parameter that might be predictive for the development of respiratory distress syndrome, with more rapid techniques being established later.

The techniques used previously have been employed to study the initial endotracheal tube aspirates of 105 babies admitted to the neonatal unit.[3 5] Differences in PC composition between groups of infants who developed respiratory distress syndrome and chronic lung disease have been examined. The aims of the study were to determine whether the PC composition of initial endotracheal tube aspirates was predictive of

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respiratory distress syndrome or chronic lung disease. In addition we report the first description of PC species composition of endotracheal tube aspirates from infants with respiratory distress syndrome.

Subjects and methods

SUBJECTS

A total of 105 infants of ≤37 weeks' gestation who were admitted onto the neonatal unit, and who required endotracheal intubation for either resuscitation or ventilation for respiratory distress syndrome, were studied. The infants were divided into the following groups, according to their developing respiratory distress syndrome (as defined clinically and radiologically) and chronic lung disease (defined as requiring supplemental oxygen at 28 days, with an abnormal chest radiograph): (1) no respiratory disease and (2) respiratory distress syndrome (a) without progression to chronic lung disease and (b) with progression to chronic lung disease. Classification was done by MAH without knowledge of the analysis results.

SPECIMEN COLLECTION

Endotracheal tube aspirates were collected by deep suction either at resuscitation, in which case no saline was used for irrigation of the endotracheal tube, or within four hours of birth at a time of normal endotracheal tube toilet. In the latter cases 0·25–0·5 ml normal saline were introduced into the endotracheal tube and allowed to dwell for approximately 10 seconds before deep suction. Traps and catheters were washed out with 1·6 ml normal saline and the washings centrifuged at 1000 *g* for 10 minutes to remove cellular debris. The supernatants were stored at −20°C until analysis.

EXTRACTION AND FRACTIONATION

Total lipids were extracted with chloroform: methanol,[6] after PC 14:0/14:0 (dimyristoyl-PC) had been added as an internal standard, and were dried under nitrogen before being dissolved in chloroform. The PC fraction was obtained by selective elution from Bondelut NH2 columns (Jones Chromatography) with chloroform:methanol (3:2, v:v).[7] Individual PC species were resolved by isocratic reverse phase high performance liquid chromatography (HPLC). A 25 cm Apex II ODS column was used, with a mobile phase of 40 mM choline chloride in 92·5% methanol, 7·5% water at 1 ml/minute.

DERIVITISATION BY DIPHENYL-1,3,5-HEXATRIENE FLUORESCENCE

Eluted peaks were quantified by postcolumn fluorescence.[4] The methanol HPLC stream was mixed with an aqueous stream of 1,6-diphenyl-1,3,5-hexatriene at 3 ml/minute, and the resultant fluorescent peaks detected by excitation at 340 nm and emission at 460 nm. The lower limit of detection for each molecular species was 200 pmol.

Demographic data for infants with measurable PC. Results are mean (SD)

	No of infants	*Gestational age (weeks)*	*Birth weight (g)*
(1) No respiratory disease	22	32·8 (2·1)	1857 (605)
(2) All babies with respiratory distress syndrome	46	31·0 (3·2)*	1703 (579)
(2a) Respiratory distress syndrome, no chronic lung disease	36	31·9 (2·8)	1885 (515)
(2b) Respiratory distress syndrome and chronic lung disease	10	27·9 (2·3)**	1049 (193)**

*$p<0·05$ compared with (1); **$p<0·0001$ compared with (1) and with (2a).

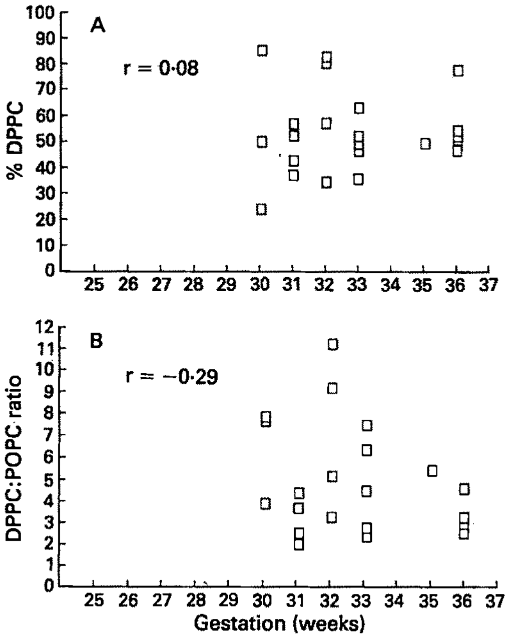

Figure 1 Infants with no respiratory disease. (A) %DPPC v gestational age and (B) DPPC:POPC ratio v gestational age. Open squares represent infants who did not develop chronic lung disease.

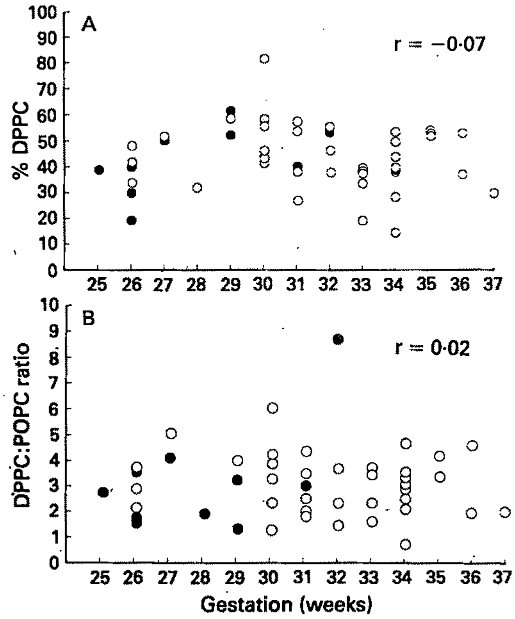

Figure 2 Infants developing respiratory distress syndrome. (A) %DPPC v gestational age and (B) DPPC:POPC ratio v gestational age. Open circles represent infants who did not develop chronic lung disease and filled circles represent infants who developed chronic lung disease. Correlation coefficients represent all infants with respiratory distress syndrome.

Anlysis of results was by the pooled Student's *t* test, and when appropriate, the construction of contingency tables, the use of the χ^2 test, and of regression analysis, using the Statgraphics software package.

Ethical approval was given by the Southampton and South West Hampshire joint ethical committee for the collection of the endotracheal tube aspirates.

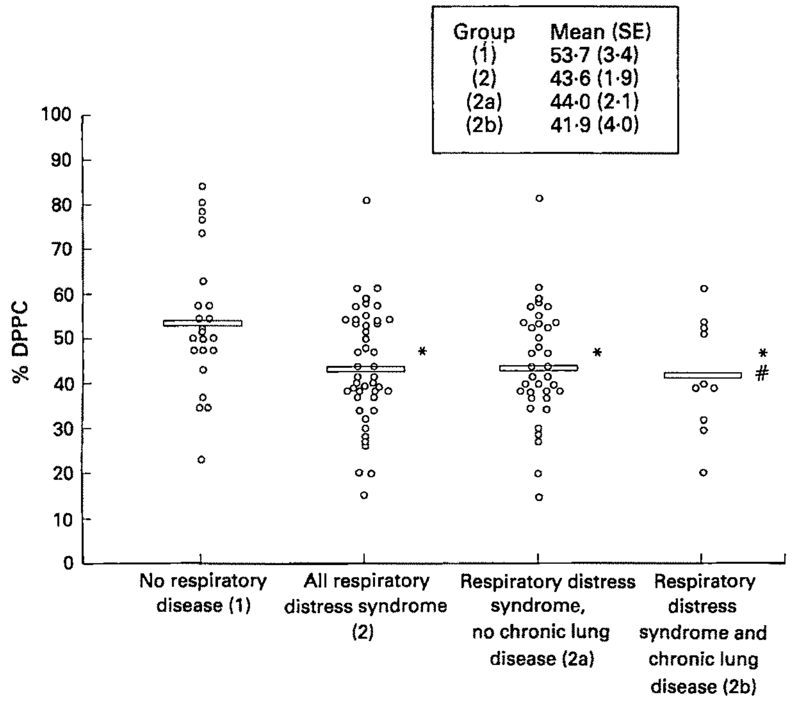

*Figure 3 %DPPC v disease. Open bars represent mean values; *$p<0{\cdot}05$ compared with (1) and #$p=0{\cdot}65$ compared with (2a).*

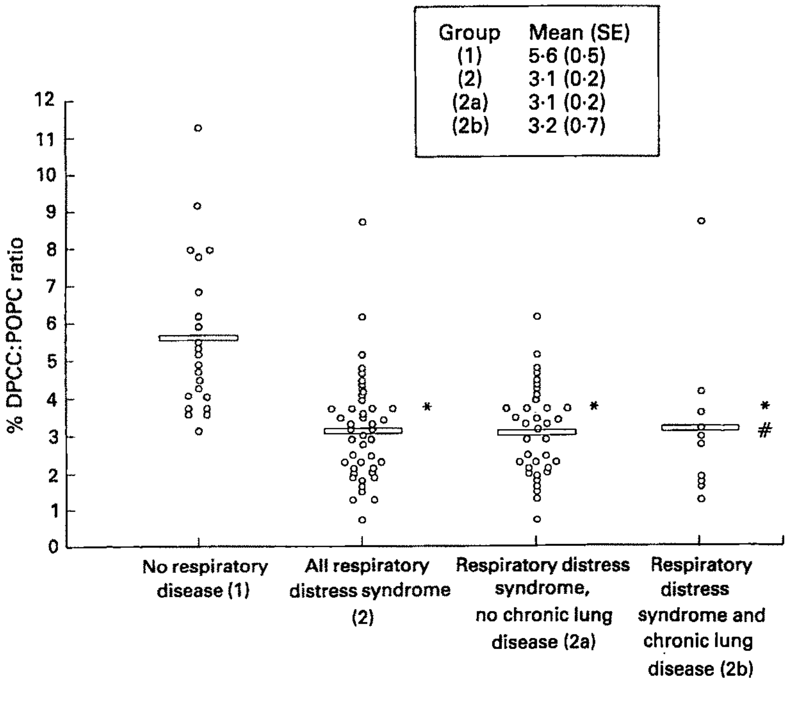

*Figure 4 DPPC:POPC ratio v disease. Open bars represent mean values; *$p<0{\cdot}005$ compared with (1) and #$p=0{\cdot}84$ compared with (2a).*

Results

Gestational age and birthweight data for infants with detectable PC are shown in the table. Of the 105 infants studied detectable PC was present in 68. Twenty two of the 37 infants in group 1 had detectable PC, as did 36 of the 50 infants in group 2(a), and 10 out of the 18 in group 2(b). The differences between the groups in the proportion of aspirates with detectable PC were not significant (χ^2 5·41 in 2 df).

As would be expected, infants developing respiratory distress syndrome were less mature than infants who did not. This difference was due mainly to those infants who went on to develop chronic lung disease, this subgroup being significantly less mature than both the 'no respiratory disease' group and the group of infants who developed respiratory distress syndrome, but did not go on to develop chronic lung disease. Indeed, the differences in gestational age between these latter two groups do not achieve significance. Similar differences between the groups are seen for birth weight, though the difference between the no respiratory disease group and the group of all infants developing respiratory distress syndrome was not significant.

The area under each derived peak of the chromatographs obtained in this study is proportional to the concentration of that particular PC species in the sample. Determination of absolute concentration was not possible as the exact volume of each aspirate sample, and the degree of dilution of the sample by the lavage saline, was not known. Results have therefore been expressed in terms of the percentage of DPPC of the total PC recovered (%DPPC), and in terms of the ratio of DPPC to POPC (DPPC:POPC ratio).

Figure 1 shows clearly that, for the infants in group 1 (no respiratory disease), there is no correlation with gestational age for either %DPPC or DPPC:POPC ratio. Similarly, fig 2 shows there is no correlation between either parameter and gestational age for infants in group 2 (respiratory distress syndrome). However, the mean values for both parameters are significantly lower for the respiratory distress syndrome group when compared with the no respiratory disease group (figs 3 and 4). These differences are not explained by the differences in gestational age between the two main groups (table) as we failed to demonstrate a correlation for either parameter with gestational age. In addition the differences persist for the 'respiratory distress syndrome, no chronic lung disease' subgroup, when it is compared with the no respiratory disease group, despite there being no significant differences in gestational age between these two groups. The mean values for both %DPPC and the DPPC:POPC ratio for the 'respiratory distress syndrome and chronic lung disease' subgroup are also significantly lower than those for the no respiratory disease group. Importantly, however, the mean values for both parameters are identical for both respiratory distress syndrome subgroups—there is no difference between the results for infants who do or do not progress to chronic lung disease.

One final important result can be seen in fig 4. All infants with an initial DPPC:POPC ratio of less than 3·0 developed respiratory distress syndrome irrespective of their gestational age. However, above this value, there is considerable overlap between groups.

Discussion

It is recognised that soon after birth premature infants, especially those ventilated for respiratory distress syndrome, may have few endotracheal tube secretions and that the detection of surfactant phospholipids in them may not be possible.[1] This was proved to be the case in this study, with one third of infants having no detectable PC in their aspirates, but no bias between groups of infants was found. The technique of deep endotracheal tube suction should ensure that smaller airway secretions are being sampled, but endotracheal tube secretion analysis will always be open to the criticism that the composition of tracheal secretions may not accurately reflect that of the alveolar surfactant pool.

With increasing gestation, the quality of pulmonary surfactant improves in terms of biochemical composition and, in animals at least, in terms of function.[8] The percentage of saturated PC species, especially of DPPC, increases at the expense of unsaturated species.[2 3 5] The amount of surfactant proteins increases[9] and the appearance of another phospholipid, phosphatidylglycerol, heralds the maturation of surfactant.[10] The data presented here show a lack of correlation between two parameters that reflect surfactant maturity (the %DPPC and the DPPC:POPC ratio) and gestational age. The lack of 'improvement' in surfactant with gestational age is at first sight surprising. However, the only human data available for PC species composition refers to just two time points during gestation—20 weeks and term[5]—serial data is not available, so the time course of 'maturation' of the PC species profile of surfactant in humans is unknown. Surfactant production pathways may mature at different rates in individual fetuses. It is possible that 'mature' surfactant production had been induced early in gestation in the premature infants that did not develop respiratory distress syndrome as part of natural variation, or perhaps as the result of obstetric intervention with antenatal dexamethasone, and that mature surfactant production had not been induced in those infants who developed respiratory distress syndrome. If this was the case then no correlation between PC composition and gestational age would be expected, but differences between groups of infants developing respiratory distress syndrome and infants not developing respiratory distress syndrome should be found.

The means of both the %DPPC and the DPPC:POPC ratio are significantly lower for the infants who developed respiratory distress syndrome compared with the infants who did not. Because of the lack of correlation between either parameter and gestational age, this suggests that a certain composition of surfactant will predisopose an infant to the development of respiratory distress syndrome, irrespective of gestational age. Of the group of infants with measurable PC in their initial endotracheal tube aspirate, all those with a DPPC:POPC ratio less than 3·0 developed respiratory distress syndrome. Though values below this could reasonably be taken as predictive for the development of respiratory distress syndrome, there is considerable overlap between groups for values above 3·0. The %DPPC shows even greater overlap between groups and would be of even less value in predicting respiratory distress syndrome.

Of the infants that developed respiratory distress syndrome, it was the lighter, less mature ones who tended to go on and develop chronic lung disease. In this study, the respiratory distress syndrome and chronic lung disease group had a mean gestational age of 27·9 weeks and a mean birth weight of 1049 g, compared with 31·9 weeks and 1885 g for the respiratory distress syndrome, no chronic lung disease group. Despite this difference in gestational age there were no differences in the %DPPC and the DPPC:POPC ratio—neither parameter was predictive for the development of chronic lung disease.

This finding does not support the suggestion that infants who later develop chronic lung disease have a poorer 'surfactant phospholipid profile' early in the course of their disease.[1] It is probable that it is not the composition of pulmonary surfactant at birth that predisposes infants to developing chronic lung disease but some other factor, or factors, associated with increasing prematurity that are responsible. Possible factors include low numbers of alveoli and, if surfactant has a role in the pathogenesis of chronic lung disease, poor surfactant function or poor continued production.[11] Alternatively, more premature infants might tend to have immature antioxidant systems or be vitamin A deficient, rendering them more prone to oxidative damage, and less able to instigate epithelial repair.[12–14]

We were unable to define a parameter predictive of respiratory distress syndrome but have shown a lack of correlation between the initial PC composition of endotracheal tube aspirates and gestational age for infants who develop respiratory distress syndrome. This suggests that a particular surfactant composition will lead to respiratory distress syndrome, irrespective of gestational age. We have also demonstrated that the initial PC composition of tracheal aspirates from infants who go on to develop chronic lung disease does not differ from those who do not develop chronic lung disease. Factors other than initial surfactant composition predipose infants to developing chronic lung disease; these factors are related to increasing prematurity.

The methodology used here proved to be sensitive in detecting individual PC species in endotracheal tube aspirates, and has great potential in the study of other aspects of neonatal respiratory disease, especially of the turnover of exogenous surfactant, and of the effects of dexamethasone in the treatment of chronic lung disease.

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Turnover of exogenous artificial surfactant

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Abstract

The turnover of the artificial surfactant Exosurf after its administration to infants with respiratory distress syndrome was studied. High performance liquid chromatography was used to compare the phosphatidylcholine (PC) composition of serial endotracheal tube secretions from three groups of infants. There were 22 infants who received two doses of Exosurf in 24 hours (group 1), 10 infants who received four doses in 36 hours (group 2), and 41 control infants who did not receive Exosurf. Two parameters were studied: (i) dipalmitoylphosphatidylcholine (DPPC), which is present in both Exosurf and endogenous surfactant, expressed as a percentage of total PC (% DPPC) and (ii) the ratio of DPPC to the entirely endogenous palmitoyloleoylphosphatidylcholine (DPPC:POPC ratio).

The administration of Exosurf produced changes in endotracheal tube aspirate PC composition that were detectable for over one week. Four doses of Exosurf in 36 hours prolonged the persistence of these changes compared with two doses in 24 hours, but the numbers of infants were small, and should not be overinterpreted. We conclude that after giving two doses of Exosurf, further doses might best be delayed until after two days, and that further clinical evaluation of dosage regimens is required.

Surfactant replacement is rapidly becoming an accepted part of the management of neonatal respiratory distress syndrome, and there are several multicentre clinical trials using exogenous surfactants in progress. There is currently little information available as to the turnover of these products in humans, information that would be a useful adjunct in determining dosage protocols.

The component of the endogenous pulmonary surfactant lipoprotein complex mainly responsible for decreasing the surface tension of the surface monolayer formed at the air-liquid interface in the alveolus is the saturated phospholipid dipalmitoylphosphatidylcholine (DPPC). In addition, pulmonary surfactant contains other phosphatidylcholine (PC) species, other phospholipids, and proteins. Exogenous surfactants fall into three main groups: artificial, natural/animal, and supplemented animal products. The artificial surfactants contain DPPC and agents to aid its adsorption to the surface monolayer, whereas the natural surfactants again contain many types of PC, including DPPC, as well as other phospholipids and proteins.

Hallman *et al*[1] and Wilkinson *et al*[2] have both used the presence of the phospholipid phosphatidylglycerol (PG) in endotracheal tube secretions of infants treated with human and artificial (ALEC) surfactants respectively to study the turnover of exogenous surfactant. The advantage of studing PG is that it is a phospholipid found only in the surfactant of infants who do not develop respiratory distress syndrome, and is not detected in the initial endotracheal tube secretions of premature infants who do develop respiratory distress syndrome.[3] It was present in the human surfactant used by Hallman's group, as this surfactant was harvested from mature amniotic fluid, and it is the second major component of ALEC, after DPPC. Thus its detection in endotracheal tube secretions of babies with respiratory distress syndrome who had been treated with one of these exogenous surfactants, could be taken as evidence of the presence of the exogenous surfactant. Hallman *et al* calculated a mean half life of the PG component of exogenous human surfactant of 30 hours. Wilkinson *et al* could not detect PG in endotracheal tube aspirates after 12 hours. They also found that the lecithin:sphingomyelin ratio of endotracheal tube secretions from these infants was acutely raised, but had returned to pretreatment values within 20 hours. However, Hallman *et al* could detect significant increases in the saturated PC:sphingomyelin ratio in treated infants, compared with control infants, for one week.[1] This has led to the suggestion that synthetic surfactants may be cleared more rapidly than natural surfactants.[4]

We have been participating in two international multicentre trials involving the artificial surfactant Exosurf (Wellcome). Exosurf contains DPPC, and hexadecanol and tyloxapol are added, to enable it to be incorporated into the surface monolayer. It is administered as a suspension in a dose of 5 ml/kg (67·5 mg DPPC/kg) via the endotracheal tube of ventilated infants. Hexadecanol is a naturally occurring alcohol, which is rapidly metabolised to palmitate, some of which could be processed to DPPC, and tyloxapol is a non-ionic surfactant. We have developed a sensitive method for the detection of different PC species in the endotracheal tube aspirates of ventilated infants and from the lungs of animals.[5 6] Two parameters have been studied: the amount of DPPC, expressed as a percentage of the total PC, and the ratio of DPPC to palmitoyloleoylphosphatidylcholine (POPC): the DPPC:POPC ratio. The DPPC recovered represents both exogenous and endogenous DPPC—it is not possible to distinguish between the two. POPC, a monounsaturated species found in relatively high concentrations in premature infants, is purely endogenously derived. The ratio of DPPC to POPC should therefore reflect the ratio of exogenous and endogenous surfactant assuming that the administration of Exosurf has no effect on POPC, an assumption that seems reasonable from studies of fetal lung remodelling of PC.[7] This information can be used to determine the rate of turnover of Exosurf.

The studies of Wilkinson and Hallman used ratios of non-specific parameters (lecithin and saturated PC, respectively) that reflect the components of the pulmonary surfactant that confer surface activity to the surfactant lipoprotein complex, to sphingomyelin. The study presented here demonstrates a novel approach to the study of exogenous surfactant, as both DPPC and POPC are specific constituents of pulmonary surfactant. Our aims were to determine the period of time over which changes in the PC composition of endotracheal tube aspirates of infants who were treated with two or four doses of Exosurf returned to that of a control group, and to determine any differences in this period between the two treatment regimens.

Subjects and methods

The controls were 41 babies admitted to the neonatal unit during the 18 months before the commencement of the studies on Exosurf (the 'Exosurf' and 'Osiris' multicentre trials), at times when the research staff were available. They were all less than 34 weeks' gestation and were ventilated from day 1 for respiratory distress syndrome diagnosed both clinically and by the typical ground glass appearance and air bronchogram on chest radiograph, by an independent observer. It was not possible to have a contemporaneous control group, because to do so would have denied those infants a treatment that preliminary reports had indicated could be beneficial to their outcome.

The treated infants fell into two groups:

GROUP 1

This group comprised 22 sequential infants less than 34 weeks' gestation who were ventilated from day 1 for respiratory distress syndrome (diagnosed as above) and who received two doses (67·5 mg DPPC/kg/dose) of Exosurf in the first 24 hours.

GROUP 2

This group comprised 10 sequential infants less than 35 weeks' gestation, ventilated from day 1 for respiratory distress syndrome (diagnosed as above), and who received four doses (67·5 mg DPPC/kg/dose) of Exosurf in the first 36 hours.

The duration of recruitment of treated infants was 22 months, from June 1989.

Exosurf was administered via the endotracheal tube, according to the Exosurf or Osiris trial protocols. The first dose was given at a mean age of 6 hours (range 1–12 hours), and doses two, three, and four were given at 12 hour intervals. Day 1 was taken as the 24 hours that included the first three doses. Dose 4 was given at 36 hours (that is, on day 2).

Endotracheal tube aspirates were collected at the time of normal endotracheal tube toilet by nursing staff. All treated infants had a predose sample collected, and each infant was sampled on each day, if they remained intubated. Approximately 0·25–0·5 ml of normal saline were introduced into the endotracheal tube, and were left to dwell for approximately 10 seconds. Deep endotracheal suction was then carried out and suction traps and catheters saved. For the treated group, aspirates were saved before the first two doses of Exosurf, and then three aspirates a day were collected and pooled to form a single daily specimen. For the control babies, three aspirates had been collected each day from approximately 4 hours of age, and pooled to form single daily specimens. Traps and catheters were washed out with 1·6 ml normal saline, and the washings centrifuged at 1000 *g* for 10 minutes to remove cellular debris. The supernatants were stored at −20°C until analysis.

Total lipids were extracted with chloroform: methanol, after PC 14:0/14:0 had been added as an internal standard, and were dried under nitrogen before being dissolved in chloroform. The PC fraction was obtained by selective elution from 100 mg Bondelut NH2 columns (Jones Chromatography) with chloroform: methanol (3:2, volume:volume). Individual PC species were resolved by isocratic reverse phase high performance liquid chromatography (HPLC). A 25 cm Apex II ODS column was used, with a mobile phase of 40 mM choline chloride in 92·5% methanol, 7·5% water at 1 ml/minute. Eluted peaks were quantified by postcolumn fluorescence. The methanol HPLC stream was mixed with an aqueous stream of 1,6-diphenyl-1,3,5-hexatriene at 3 ml/minute, and the resultant fluorescent peaks detected by excitation at 340 nm and emission at 460 nm. The lower limit of detection for each molecular species was 200 pmol.[8–10]

The arterial:alveolar (a:A) ratio, as calculated from the alveolar gas equation, is an index of the severity of respiratory distress syndrome with values falling as severity increases. It was calculated at the time of the initial aspirate for all infants.

Comparison between groups was with the Mann-Whitney U test for the PC analysis data, and both the pooled Student's t test and the Mann-Whitney U test for the demographic and a:A ratio data. The χ^2 test was used to compare the proportion of 'successful' samples in each group. The Statgraphics software package was used throughout.

Ethical approval was given by the Southampton and South West Hampshire joint ethical subcommittee for both the Exosurf and Osiris trials, and for the collection of endotracheal tube aspirates.

Results

The initial a:A ratios, birth weight, and gestational age for the two treatment groups and the controls are shown in table 1. There were no significant differences for any variable between any of the groups. One control infant and one infant from group 1 died during the course of the study.

Table 2 shows the number of infants on each day who had detectable PC in their endotracheal tube aspirates and the number of babies intubated on each day.

Figure 1 shows a typical chromatograph obtained from an infant during this study. She had received two doses of Exosurf three days previously. The area under each peak is proportional to the concentration of that particular molecular species, but it is not possible to calculate absolute concentrations as accurate estimation of the volume of endotracheal tube secretions recovered and the degree of their dilution by the normal saline lavage is not feasible. Results for a particular PC molecular species are therefore expressed as the percentage that species contributes to the total amount of PC recovered.

Figure 2 shows the percentage DPPC (%DPPC) in serial endotracheal tube aspirates from an infant who received three doses of Exosurf in the first 24 hours, but who, because of tube blockage, was reintubated with clean endotracheal tubes, three times in the 36 hours after the final dose of surfactant had been given. Despite this repeated change of endotracheal tube, the %DPPC present in the endotracheal tube secretions remained unaffected. Although this evidence is anecdotal, this infant is representative of several infants who required reintubation after completion of Exosurf administration. In addition we also observed infants who were not reintubated and in whom a rapid fall towards control values of both %DPPC and DPPC:POPC ratio occurred.

Figure 3 shows the %DPPC in the endotracheal tube for controls and both treatment groups. The administration of one dose produced a highly significant increase in the %DPPC, compared with the day 1 controls. A second dose caused a further rise, and in many cases the amount of DPPC recovered was so large that it spread during HPLC and swamped the other types of PC completely. These specimens were allocated a %DPPC of 100%, although other PC species were almost certainly present, but in

Table 1 Demographic data and initial a:A ratios. Results are median (range)

	Controls (n=41)	*Group 1 (2 doses) (n=22)*	*Group 2 (4 doses) (n=10)*
Gestation (weeks)	29·0 (25–33)	27·5 (24–33)	28·5 (24–34)
Birth weight (g)	1160 (690–2240)	1095 (700–1840)	1090 (760–2450)
a:A ratio	0·13 (0·07–0·46)	0·15 (0·06–0·44)	0·10 (0·04–0·19)

Table 2 Numbers of infants in each group

	Controls		*Group 1*		*Group 2*	
	Intubated	*Samples*	*Intubated*	*Samples*	*Intubated*	*Samples*
Before first dose/day 1	41	26	22	7	10	4
Before second dose	—	—	22	13	10	8
Day 2	38	21	21	17	10	9
Day 3	37	18	21	20	10	8
Day 4	34	16	20	16	10	8
Day 5	33	18	18	12	8	6
Day 6	27	15	16	12	8	5
Day 7	24	14	14	6	7	5
Day 8	21	10	11	8	6	2
Day 9	19	11	11	6	5	3
Day 10	19	9	11	7	5	4

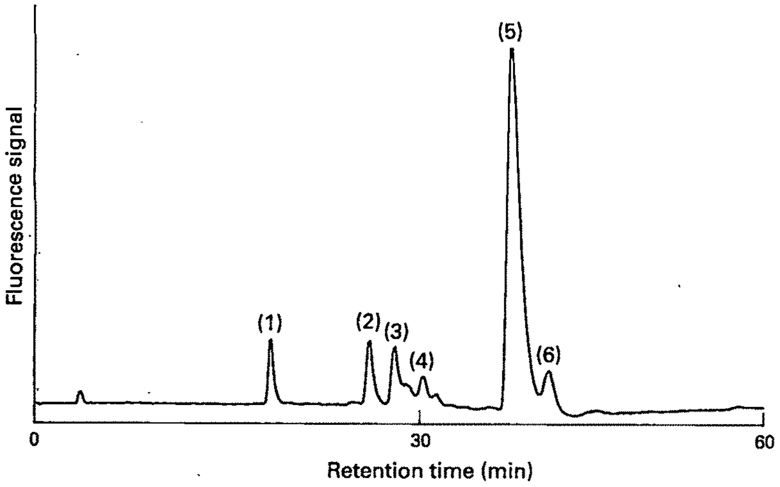

Figure 1 Typical chromatograph three days after administration of two doses of Exosurf. Peaks: (1) Internal standard, PC 14:0/14:0 (dimirystoyl-PC); (2) PC 14:0/16:0 (mirystoylpalmitoyl-PC); (3) PC 16:0/16:1 (palmitoylpalmitoleoyl-PC); (4) PC 16:0/18:2 (palmitoyllinoleoyl-PC; (5) PC 16:0/16:0 (dipalmitoyl-PC); (6) PC 16:0/18:1 (palmitoyloleoyl-PC).

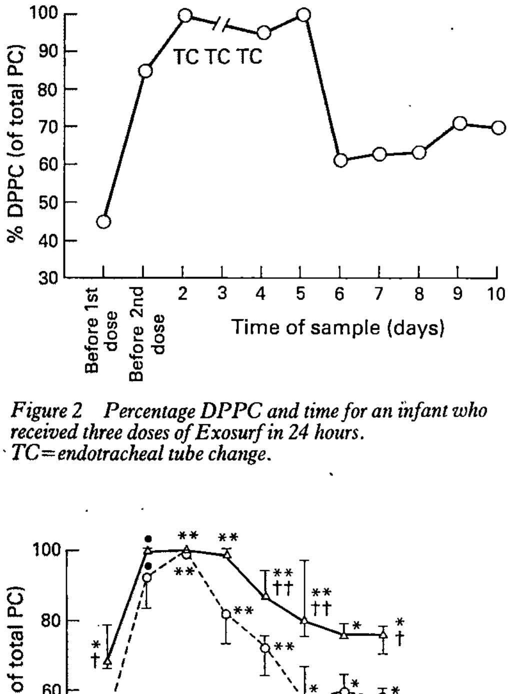

Figure 2 Percentage DPPC and time for an infant who received three doses of Exosurf in 24 hours. TC=endotracheal tube change.

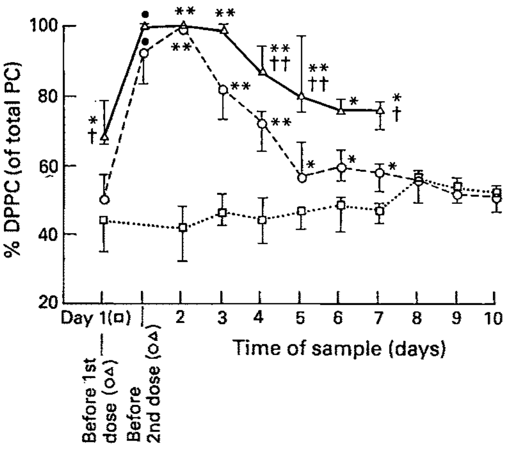

*Figure 3 Percentage DPPC and time for group 1 (circles), group 2 (triangles), and controls (squares). Bars represent lower and/or upper quartiles; ●=$p<0{\cdot}001$, compared with day 1 controls; **$p=<0{\cdot}001$, compared with same day controls; *=$p<0{\cdot}05$, compared with same day controls; ††=$p<0{\cdot}01$, compared with same day group 1 infants; †=$p<0{\cdot}05$, compared with same day group 1 infants.*

such comparatively small amounts as not to be detectable.

Significant differences, between group 1 and controls for the %DPPC, persisted up to and including day 7. The %DPPC was significantly higher in group 2 specimens taken before the first dose compared with both controls and group 1. However, similar dramatic rises in %DPPC to those seen for group 1 were demonstrated. As infants recovered the number of infants who remained intubated, and from whom samples could therefore be taken, fell (see table 2). Beyond day 7, the numbers in group 2 were very small and so have not been included in this analysis. Significant differences between group 2 and controls persisted for the whole seven days. In addition group 2 infants had a %DPPC that was significantly greater than group 1 infants on days 4, 5, and 10.

Figure 4 compares the DPPC:POPC ratio for both treatment groups and controls. The highest recorded DPPC:POPC ratio was 137. Specimens in which DPPC swamped the other types of PC were allocated a DPPC:POPC ratio of 150. A rise in the DPPC:POPC ratio compared with controls similar to that observed for the %DPPC occurs and, for group 1, is maintained to a significant level until day 4, but with a trend persisting until day 7. For group 2 the ratio remains significantly high compared with controls for six days. Group 2 had a significantly greater DPPC:POPC ratio compared with group 1 on days 4, 5, and 7.

MISSING DATA

As has been previously reported,[1] it is not always possible to detect phospholipids in endotracheal tube aspirates if the volume of aspirate is low. This is a particular problem in the first 24–48 hours. For this reason, not all samples could be successfully analysed. However, there were no significant differences in the proportion of 'successful' samples between the groups after χ^2 analysis of appropriate contingency tables.

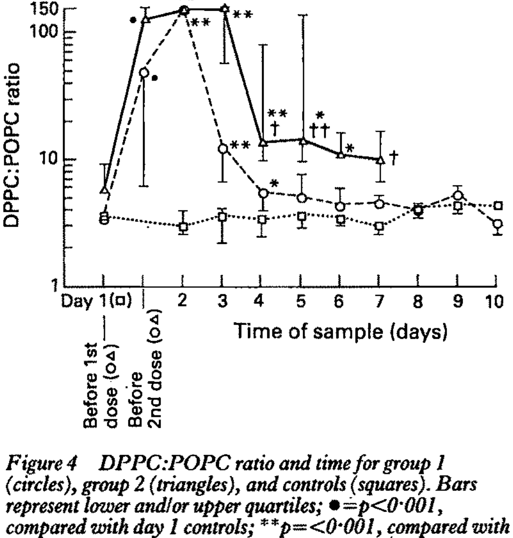

Figure 4 DPPC:POPC ratio and time for group 1 (circles), group 2 (triangles), and controls (squares). Bars represent lower and/or upper quartiles; $\bullet = p<0{\cdot}001$*, compared with day 1 controls;* $^{**}p=<0{\cdot}001$*, compared with same day controls;* $^{*}=p<0{\cdot}05$*, compared with same day controls;* $\dagger\dagger=p<0{\cdot}01$*, compared with same day group 1 infants;* $\dagger=p<0{\cdot}05$*, compared with same day group 1 infants.*

Discussion

When infants were given two doses of Exosurf within the first 24 hours a significant increase in the %DPPC could be detected for the first week of life when compared with controls. The ratio of DPPC:POPC, which reflects the ratio of exogenous to endogenous surfactant, showed a similar trend, with differences significant until day 4. These findings are entirely in keeping with those of Hallman *et al* who, using human surfactant, detected significant increases in the saturated PC:sphingomyelin ratio, compared with control infants, for 1 week.[1] These data contradict the suggestion that artificial surfactants are cleared more rapidly from the lung than natural surfactants.[4]

When four doses of Exosurf were given in 36 hours similar acute changes in both %DPPC and DPPC:POPC ratio were noted. The number of infants who received four doses of Exosurf was small (n=10) and was reduced after five days as babies were extubated. In addition, the initial median %DPPC for group 2 was significantly greater than either the control group, or group 1, though the initial a:A ratio data suggest that the group 2 infants were at least as severely affected as the others, and there were no significant differences between the initial DPPC:POPC ratios. These data should not be overinterpreted, but they do show an interesting trend: the %DPPC was significantly raised over controls throughout the seven days, and the DPPC:POPC ratio was raised significantly until day 6. There was also a persisting difference for both %DPPC and the DPPC: POPC ratio when the two treatment groups were compared. This difference persisted beyond the time that would be expected because of the later administration of the third and fourth doses.

It is possible that analysis of composition of PC from the endotracheal tube might only reflect the PC content of the secretions lining the inside of the endotracheal tube, and that endotracheal tube secretions do not reflect lung fluid itself. However, babies such as the baby whose results are illustrated in fig 2 and who needed reintubation after completion of the surfactant dose did not show the dramatic fall in %DPPC that would be expected if all that was being measured was the content of fluid lining the endotracheal tube. The other compelling piece of evidence is that in most of the aspirates species of PC other than DPPC were detected, indicating that at least part of the sample is derived from the lower respiratory tract.

The results for both treatment groups emphasise that merely replacing the surface active material neither prevents respiratory distress syndrome nor does it cure it. The %DPPC and DPPC:POPC ratio are both very high on days 2, 3, and 4 and exceed values reported for term infants who did not develop respiratory distress syndrome,[5] but all of these infants were being ventilated for the syndrome. However, recently published data do show a reduction in mortality from respiratory distress syndrome.[11–13]

The persistence of the changes in the PC composition could be the result of the exogenous surfactant just inertly lining the alveolar air-space. However, animal studies suggest that the situation is much more dynamic. Alveolar wash recovered only 19% of radiolabelled PC from exogenous sheep surfactant from preterm ventilated sheep three hours after treatment.[14] Altogether 55% was recovered from lung tissue, suggesting a rapid intake, presumably by type II alveolar cells, after administration. Similar results were obtained three hours after labelled PC in exogenous sheep, calf, and supplemented bovine surfactant was given to 3 three day old rabbits.[15] It is likely that the DPPC from Exosurf is taken up by type II alveolar cells and recycled. Perhaps the most unusual aspect is the persistence of the changes. Studies on 3 day old rabbits showed that labelled exogenous rabbit surfactant was cleared from the lungs at a rate that was almost five times slower than in adult rabbits.[16] Similar age related differences in humans might account for the persistence of PC composition changes.

The number of doses of an exogenous surfactant, and their timing, will have important cost implications. At present the only published data for Exosurf refers to regimens using one or two doses,[11-13] and it is likely that the analysis of data from the Osiris trial in which two and four dose regimens have been compared, will take some time to be completed. Although a regimen of four doses in 36 hours prolonged the period during which changes in the PC composition in the endotracheal tube could be detected to at least six days, large changes were detectable for at least four days when two doses were given in 24 hours. We suggest, therefore, that if more than two doses of Exosurf are to be considered, then delaying the administration of subsequent doses until after day 2 might represent a logical step. Further clinical evaluation of the timing of dosage regimens is required.

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Plasma hypoxanthine: a marker for hypoxic-ischaemic induced periventricular leucomalacia?

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Abstract

Cerebral ischaemia of the immature brain may result in cavitating periventricular leucomalacia (PVL), an important association of cerebral palsy. Hypoxanthine measured by high performance liquid chromatography was used as a marker of peripartum hypoxia and ischaemia in 116 infants at risk of PVL. PVL was detected by ultrasound. The 81 infants who were unaffected had median (range) gestation of 30 weeks (24–32), weight of 1336 g (724–3790), and a plasma hypoxanthine concentration of 7·8 μmol/l (2·4–48·9). The seven infants who had cavitating PVL had a median gestation of 28 weeks (26–30), weight of 1165 g (682–1860), and a hypoxanthine concentration of 31·9 μmol/l (7·1–149). Cavitating PVL was significantly dependent only on hypoxanthine when controlling for the effects of weight and gestation. This suggests that peripartum hypoxia-ischaemia may be one of the aetiological factors in cavitating PVL. Oxidation of hypoxanthine during reperfusion generates free radicals which may contribute to the tissue destruction of PVL. The association of hypoxia-ischaemia with PVL suggests that PVL may be modified by reducing free radical activity.

Cavitating periventricular leucomalacia (PVL) is an important association of cerebral palsy and is found in 7–15% of babies under 1500 g at birth.[1] Between 47% and 80% of infants with parenchymal cavitation develop abnormalities of neuromuscular tone and posture with or without cognitive impairment.[2–5] PVL is a pathological term which has become synonymous in clinical terminology with high resolution sonographic abnormalities detected in the neonatal period[6] because the parenchymal echodensities and echolucencies detected by ultrasound have been correlated with pathological abnormalities at necropsy.[7 8] Ultrasound has led to improved understanding of the incidence, timing, and clinical associations of PVL.[1 9 10]

Risk factors associated with PVL such as prematurity,[1 7 9] very low birth weight,[1 9] antepartum haemorrhage,[9 10] asphyxia,[9–12] respiratory distress requiring mechanical ventilation,[9–11] and septicaemia,[9] may result in hypoxaemia and hypotension with resultant tissue hypoxia and ischaemia of the vulnerable periventricular 'watershed zones' of the immature brain.[13]

The purine metabolite hypoxanthine is a marker of tissue hypoxia or ischaemia.[14 15] Accumulation of hypoxanthine has been detected in cord blood from asphyxiated babies[16–18] and in perfusate from ischaemic organs.[19–21] The postischaemic catabolism of accumulated hypoxanthine results in the generation of tissue damaging, oxygen derived, free radicals by the action of an endothelial enzyme, xanthine oxidase, and oxygen.[22] Hypoxic-ischaemic injury to the brain has been reported in animal models and tissue protection demonstrated by the administration of free radical scavengers.[23–25]

To test the hypothesis that an increase in hypoxanthine (as a marker of hypoxia) is associated with PVL, we have examined an 'at risk' population of preterm infants by measuring plasma hypoxanthine concentrations at birth and relating these to the subsequent development of cavitating PVL. We have assumed that cavitation represents the severest degree of ischaemic injury and therefore the severity of the hypoxic insult would be more likely to result in increased circulating hypoxanthine.

Patients and methods

Babies between 24 and 32 weeks' gestation admitted to the Regional Neonatal Intensive Care Unit were studied. Plasma hypoxanthine was measured in samples obtained from cord blood or as soon as possible after admission to the unit. Care was taken to ensure that samples were taken by large needle puncture of either cord artery or vein[17] or by an indwelling arterial line or clean venesection. Samples were rapidly separated and stored at −30°C to avoid leakage of erythrocyte hypoxanthine. Haemolysed samples were discarded.

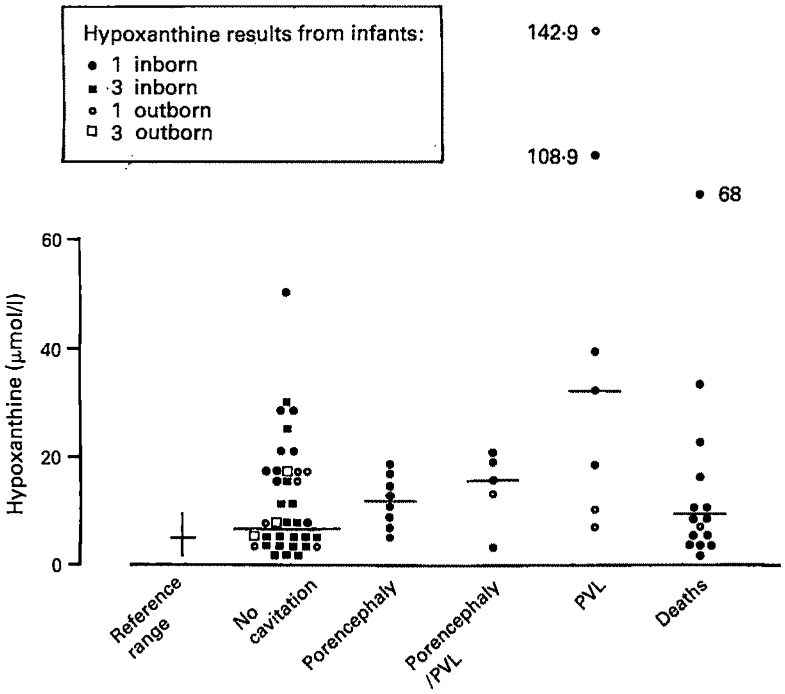
Serial cranial ultrasound (ATL Ultramark 4 with a 7·5 MHz transducer) was performed from admission and then at least weekly until discharge. Parenchymal echodensities (of equivalent echodensity to the choroid plexus) seen in both coronal and parasagittal planes were regarded as precavitating PVL. Three groups of echolucencies were identified: porencephaly (lucency widely communicating with the ventricle), cavitating PVL (single or multiple lucencies occurring 2–3 mm from the ventricular wall), and porencephaly with associated PVL (porencephaly with surrounding non-communicating lucencies either single or multiple occurring 2–3 mm from the porencephalic cavity wall).

Hypoxanthine was measured by reverse phase high performance liquid chromatography[26] using a Waters model 481 LC spectrophotometer. The column (8×100 mm inside diameter) was packed with a Nova-Pak C18 4 μM cartridge (Waters), and a Waters Guard-Pak μBondapak precolumn insert was used. The plasma samples were deproteinised by heating for 2 minutes in a boiling water bath and then ultracentrifuged for 20 minutes at 23500 *g* with a MSE Superspeed 65 centrifuge. The supernatant was diluted 1:2 with the mobile phase, 0·004M potassium dihydrogen orthophosphate, adjusted to pH 5·8, and injected in 20 µl aliquots at a flow rate of 0·5 ml/min. Detection of the eluted compounds was at 254 nm. The effluent peaks were identified by their retention times determined by known standards and confirmed by enzymic digestion using xanthine oxidase (Merck). Activity of xanthine oxidase: 0·4 enzyme unit (EU)/mg protein with hypoxanthine as substrate and 0·8 EU/mg protein with xanthine as substrate). Quantification of the peaks was computed from standard pure compound peaks before and after each 6–8 sample injections. The standards (hypoxanthine and xanthine) were supplied by Merck.

The assay had a recovery of >95% of known concentrations of hypoxanthine from 5 µmol/l to 100 µmol/l and the coefficient of variation was 5·6%. Results of hypoxanthine were not available until 6–8 weeks after birth and this avoided observer bias in the diagnosis of PVL. The reference plasma hypoxanthine concentration in our unit was 4·7 µmol/l (95% confidence interval (CI) 3·7 to 5·7) with the upper limit (2 SD) of 9·5 µmol/l determined from cord arterial blood obtained from 22 unstressed term infants delivered at elective caesarean section (figure).

Statistical analysis was by Mann-Whitney U test for comparison of non-parametric data, and multiple logistic regression analysis was used to control for confounding variables when dichotomous outcome variables were evaluated. The SPSS-X 3·1 statistical package on an IBM 3081 mainframe computer was used.

Informed parental consent was obtained for all patients studied and ethical approval was granted by the hospital ethical committee for the study.



Plot of plasma hypoxanthine concentration in 116 preterm babies. Horizontal bars indicate the median value for each group. The reference range indicated on the left is the mean (2 SD) of cord plasma hypoxanthine of a group of 22 term babies delivered by elective caesarean section.

Table 1 Details of preterm infants examined by cerebral ultrasound after postpartum plasma hypoxanthine sampling

	No cavitation (n=81)	*Porencephaly (n=8)*	*Porencephaly/ PVL (n=5)*	*PVL (n=7)*
Gestation (weeks):				
Median	30	28*	27*	28*
Range	24–32	26–31	27–29	26–30
Weight (g):				
Median	1336	1135	850*	1165
Range	724–3790	682–1860	758–1432	682–1860
Hypoxanthine (µmol/l):				
Median	7·8	12·3	14·7	31·9**
Range	2·4–48·9	7·4–18·4	2·9–19·4	7·1–142·9
Sample time (min):				
Median	100	107	85	76
Range	0–972	0–308	0–566	0–588

Compared with non-cavitation group: *p<0·05; **p<0·005 (95% CI 4·0 to 81·0).

Results

Of the 116 babies studied, 15 died within 14 days without developing cavitating PVL (four had echodensities). Of the 101 survivors, 81 did not develop parenchymal cavitation but four of them had parenchymal echodensities which resolved. The remaining 20 (17·2%) babies developed parenchymal cavitation: seven of these had cavitating PVL alone, eight had porencephaly alone, and five had porencephaly with associated PVL.

The two groups with porencephaly, with or without PVL, had higher median hypoxanthine concentrations than the unaffected group but the differences were not significant (table 1). The group with PVL alone had a median hypoxanthine which was significantly higher at 31·9 µmol/l (p<0·005). This difference persisted after adjusting for gestation and weight (p<0·05) by multiple logistic regression, with PVL as the dependent variable, and weight, gestation, and hypoxanthine as the independent variables. A measure of the risk of developing PVL, the odds ratio (OR), was calculated from the regression model. The OR (with 95% CI) for developing PVL was 1·89 (1·01 to 3·53) for every 10 µmol/l increase of hypoxanthine (p<0·05). The unit change of the independent variable is arbitrarily selected for convenience, such as one week for gestation or 10 µmol/l for hypoxanthine.

No significant dependence on hypoxanthine (while controlling for weight and gestation) could be demonstrated for porencephaly alone (OR 0·75; 95% CI 0·43 to 1·85) or porencephaly with associated PVL (OR 1·52; 95% CI 0·97 to 2·38).

The details of babies who developed parenchymal cavitation, including the time delay in sampling of blood for hypoxanthine, are shown in table 2 and the figure demonstrates the plot of hypoxanthine concentrations for each group. An increased concentration of hypoxanthine within two hours of birth, thought to indicate antenatal hypoxia,[16 27] was found in all three groups of parenchymal cavitation: 4/7 of the group with PVL, 4/8 of the porencephaly group, and 3/5 of the porencephaly and associ-

Table 2 Details of patients with parenchymal cavitation

Case No	*Gestation (weeks)*	*Weight (g)*	*Sex*	*Birth*	*Sample time (min)*	*Hypoxanthine (μmol/l)*
PVL alone						
1	30	1420	M	Inborn	76	39·0
2	26	726	F	Inborn	Cord	18·0
3	27	682	F	Inborn	Cord	31·9
4	28	998	M	Inborn	Cord	108·9
5	26	1220	M	Outborn	420	142·9
6	29	1860	M	Outborn	290	9·5
7	28	1165	M	Outborn	558	7·1
Median	28	1165			76	31·9
Porencephaly alone						
13	28	1150	M	Inborn	90	11·4
14	28	1120	M	Inborn	84	14·3
15	29	1382	M	Inborn	120	16·6
16	26	762	M	Inborn	150	8·0
17	28	1072	M	Inborn	308	7·7
18	27	1082	M	Inborn	170	18·4
19	31	1588	F	Inborn	Cord	7·4
20	31	1616	M	Inborn	Cord	13·2
Median	28	1135			107	12·3
Porencephaly and PVL						
8	27	758	M	Inborn	Cord	19·4
9	27	900	F	Inborn	85	14·7
10	27	812	F	Inborn	85	18·9
11	28	1220	F	Inborn	Cord	2·9
12	27	1432	M	Outborn	566	12·7
Median	27	900			85	14·7

ated PVL group. An increase in hypoxanthine within two hours of birth was also found in 20/43 babies in the non-cavitating group.

In some of the babies, an increased concentration was found at later sampling times and may have been due to postnatal events, although all patients received intensive care support throughout the period from delivery to sampling to minimise hypoxia or ischaemia. The delay in sampling was due to either postnatal transfer (4/20 with parenchymal cavitation or 21/81 with no cavitation) or the delay in gaining vascular access for blood sampling if cord blood was not available. No significant differences in sampling time were detected between the groups with cavitation and the group with no cavitation. Although there was a trend to lower concentrations of hypoxanthine with increasing time delay to sampling this was not significant (Spearman correlation coefficient=−0·1295; p>0·1), and this suggests that the normal concentrations of hypoxanthine in the non-cavitation group was not merely due to delay in sampling after delivery.

The group of 15 babies who died had a median (range) gestation of 27 weeks (24–31) and weight of 850 g (565–1260). In this group the median hypoxanthine was 8·6 μmol/l (2·4–68·3) and the sampling time was 78 min (0–380) (see figure).

Discussion

Events such as antepartum haemorrhage and clinical perinatal asphyxia have been associated with subsequent development of PVL,[9–12] and parenchymal echodensities detected by ultrasound may appear within three days of birth,[1] suggesting that many cases are related to peripartum events. PVL is a manifestation of cerebral hypoxia-ischaemia,[28] and an increased concentration of plasma hypoxanthine is a biochemical marker of peripartum hypoxia.[16–18] The association we have found between increased early plasma hypoxanthine and the development of PVL gives indirect evidence to support the hypothesis that cerebral hypoxia-ischaemia may induced PVL in preterm infants.

There is conflicting evidence for an association between increased concentrations of plasma hypoxanthine and adverse clinical outcome in term babies. Increased cord hypoxanthine or hypoxanthine excretion is found in asphyxiated babies with a reduced 'optimality score'[16] or abnormal neurological signs during the first week of life but there is considerable overlap with unaffected babies.[16 18] Neurological assessment at 2 years could not be correlated with cord hypoxanthine in term babies[29] but we are not aware of any evidence for preterm babies. The fetal cerebral oxygen uptake rapidly decreases with falling arterial oxygen saturation, especially in combination with acidaemia,[30] and so the effect of global hypoxaemia on the vulnerable periventricular watershed zones could affect the fetal and preterm brain more than the term infant with more developed periventricular anastamoses.[13]

Our study may have underestimated any association between increased plasma hypoxanthine and PVL because delay in sampling (including outborn babies) was unavoidable in many babies and also because subsequent postnatal hypoxic-ischaemic insults after the admission sampling would not have been detected by hypoxanthine measurements: any increase due to birth asphyxia might have returned to normal giving a false negative association with PVL. On the other hand normal concentrations detected in babies without PVL might have been due to delayed sampling. We found no correlation between sample time and hypoxanthine concentration and this suggests that in the non-cavitating group the normal value of hypoxanthine was not due to delayed sampling. The half life of plasma hypoxanthine is three minutes in rabbits[31] and 40 minutes in pigs after a hypoxic-ischaemic episode[32]; in term babies increased concentrations may be detected for two hours after asphyxia[16 27] and in preterm babies increased values have persisted for 24 hours after an hypoxic episode.[14] Plasma hypoxanthine is likely to be trapped in tissues because of inadequate tissue perfusion and circulation; increased values may therefore be detected for some time after the hypoxic insult, until adequate circulation is re-established. This may explain the marked increase in hypoxanthine (142·9 μmol/l) at seven hours in one baby in the PVL group, despite establishing adequate oxygenation and blood pressure after an emergency caesarean section for footling breech presentation (table 2, case 5).

The degree and timing of the hypoxic episode would influence the magnitude and duration of hypoxanthine increases. An insult occurring in the peripartum period may not therefore have been detected by admission sampling of outborn babies at six to eight hours. Two of the lowest values of hypoxanthine in the PVL group were recorded from outborn infants. About half of the babies from our study who developed any form of parenchymal cavitation had evidence of birth asphyxia, evidenced by increased concentrations of hypoxanthine (greater than 2 SD from the mean: 9·5 μmol/l) within two hours of birth. This would suggest that the hypoxic-ischaemic insult occurring antenatally might be associated with later development of parenchymal cavitation.

Increased hypoxanthine has been detected after postnatal events such as pneumothorax, mechanical ventilation for severe respiratory distress syndrome, shock, and necrotising enterocolitis (own observations). Global hypoxia increases plasma hypoxanthine (probably arising from organs with a lower threshold for purine degradation, such as the liver and gut) whereas focal ischaemia within an organ, especially the brain with a higher threshold for purine degradation, may not increase systemic plasma hypoxanthine sufficiently to be detectable by remote sampling.[33] Plasma hypoxanthine measured in peripheral plasma is therefore a marker of global hypoxia but this is likely to be associated with global cerebral hypoxia-ischaemia. Cerebral hypoxia and ischaemia may therefore be a mechanism of parenchymal injury in pneumothorax, severe respiratory distress requiring mechanical ventilation and shock.

In our study, plasma hypoxanthine was only slightly increased in the two groups in which porencephaly was found. This could be because early sampling did not detect a later postnatal event or because porencephaly may result from different pathogenic mechanisms. First, localised parenchymal infarction secondary to the presence of a contiguous large blood clot and release of vasoactive substances such as thromboxane, prostacyclin,[34] or potassium[35] may lead to porencephaly rather than PVL. Second, parenchymal venous infarction due to obstruction of veins of the periventricular white matter by distension of the germinal matrix and ventricles after periventricular haemorrhage, could also cause porencephaly and possibly PVL.[36] PVL associated with porencephaly is likely to be secondary to the pathogenic mechanisms responsible for porencephaly. Not all cases of PVL occur in association with periventricular haemorrhage and it is therefore likely that PVL is due to local or generalised cerebral ischaemic infarction, and porencephaly due to local ischaemia or venous infarction. Unfortunately sampling of plasma hypoxanthine from the cerebral venous drainage is not possible in premature babies, and therefore it is difficult to detect direct evidence of local or even global cerebral ischaemia based on hypoxanthine concentrations. Cerebral arteriovenous hypoxanthine difference increases significantly during severe asphyxia in the fetal lamb brain, even though there is a high threshold for degrading energy rich intracellular purines.[33]

Hypoxanthine is also a free radical generator[37] and this recognition has resulted in renewed interest in the hypoxic-ischaemic mechanism of tissue injury. Free radical induced tissue damage has been demonstrated secondary to excessive production of free radicals by the xanthine oxidase-hypoxanthine reaction.[22] If hypoxia-ischaemia and free radical generation are aetiological factors in ischaemic disorders of the infant brain, this suggests possible strategies for intervention. Prophylactic inhibition of xanthine oxidase in preterm babies at risk of PVL may reduce the free radical generation after reperfusion/reoxygenation and may therefore limit the extent of tissue destruction. Allopurinol and its major active metabolite oxypurinol are specific inhibitors of xanthine oxidase that have been shown to limit tissue damage due to free radical activity.[23 24] Other free radical scavengers may also have a place in ameliorating damage.[25] Difficulties would be encountered in antenatal hypoxia, but peripartum and postpartum hypoxic-ischaemic insults may be more amenable to therapeutic intervention.

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Somatosensory evoked potentials and outcome in perinatal asphyxia

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Abstract

Somatosensory evoked potentials (SEP) can be measured in the term newborn infant and given an index of function in the areas of the brain most likely to be damaged in perinatal asphyxia. We studied the median nerve SEP in 30 asphyxiated term infants over the course of their encephalopathy and until discharge from the neonatal unit. Three types of response were noted: normal waveform, abnormal waveform, or absence of cortical response.

Follow up of the survivors was undertaken at a mean age of 12 months by means of a Griffiths' assessment and neurological examination. Nine infants died of their asphyxial illness and one of spinal muscular atrophy. Of the 20 survivors, three have cerebral palsy, four have minor abnormalities, and 13 are neurodevelopmentally normal.

There was a close correlation between outcome and SEP. All 13 infants with normal outcome had normal SEP by 4 days of age, whereas those with abnormal or absent responses beyond 4 days had abnormalities at follow up.

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Perinatal asphyxia remains the single most important cause of neurodevelopmental handicap in the term newborn infant. The prognosis of the surviving infant is of importance both to the paediatrician deciding on follow up and physiotherapy and to the parents. The literature contains many reports of attempts to assess the prognosis using clinical examination, biochemical measurements, Doppler ultrasound assessment of cerebral blood flow velocity, electroencephalography (EEG), and computed tomography.[1–7] Each of these techniques is subject to inaccuracy. Two previous papers have discussed the use of somatosensory evoked potentials (SEP) in perinatal asphyxia on small numbers of infants.[8 9]

We undertook to investigate the use of SEP in the prognostic assessment of a group of asphyxiated term infants. The parts of the brain most vulnerable to damage in this condition are the cortex, the immediate subcortical white matter, and the periventicular white matter.[10] The somatosensory pathway traverses these areas and it seems reasonable to suppose that damage to these areas may be reflected in abnormalities of SEP.

Patients and methods

Between May 1987 and December 1988 term infants were recruited from the neonatal unit of Leicester Royal Infirmary after a full explanation to the parents. Ethical approval had been obtained from the local ethical committee. The infants were selected on the basis of term delivery; the presence of adverse perinatal factors consistent with an asphyxial insult, such as an abnormal cardiotocograph, low scalp pH, cord prolapse or uterine rupture; and the presence of abnormal neurological findings in the neonatal period consistent with an asphyxial insult. The hypoxic-ischaemic encephalopathy was graded according to the description by Levene *et al*[11] modified from the Sarnat scheme.[2]

Thirty term infants with a mean gestational age of 39·5 weeks were recruited. Five were very small for dates (<3rd centile). All had clinical evidence of perinatal asphyxia and, in addition, one was subsequently shown to have spinal muscular atrophy and two had group B β-haemolytic streptococcal septicaemia, one of whom also had meningitis. Eight of the infants had mild encephalopathy and were neurologically normal by 3 days of age; six of the infants were moderately encephalopathic with more noticeable abnormalities of tone and seizures; the remaining 16 infants were severely asphyxiated. In addition, during the time of the study, there were two other infants fulfilling the enrolment criteria who did not take part. One infant died at 3 hours of age before he could be studied and the parents of one infant did not give consent for the study.

Median nerve SEP were recorded as soon as possible after admission to the neonatal unit and until resolution of the encephalopathy or death. Planned intervals between studies were every two days in the first week and twice a week thereafter. A hand held stimulator device delivering 1024 electrical impulses of 0·1 ms duration over the median nerve at a frequency of 5 Hz was employed. Normally three runs on each median nerve would be recorded. The response in the first 100 ms (sweep time) after each stimulus was recorded from silver/silver chloride skin surface electrodes over the cervical cord (Cv2) and the contralateral cortex (C″3 and C″4) with a reference electrode in a midline frontal position (Fpz). An earth electrode was placed on the forearm. When this arrangement failed to evoke measurable potentials, the stimulus was delivered at 1 Hz for 256 or 512 stimuli and the sweep time increased to 200 ms. The signals were fed to a Medelec Sensor evoked potential system for amplification, filtering using a 10–3000 Hz bandpass, averaging, and display. Sleep state could not be accurately assessed and would have been distorted in many of the infants by the use of anticonvulsants, but a visual inspection of behaviour was made. The acutely ill infants had regular estimations of blood glucose performed by reagent strips (BM-Test 1–44, BM Diagnostics) to exclude hypoglycaemia which may effect evoked potentials.[12] Oxygen monitoring by transcutaneous electrodes ensured that recordings were not done in the presence of hypoxia.

The SEP traces obtained were stored on an Apple IIe microcomputer for later analysis. The features assessed in the SEP were the shape of the cervical and cortical waveforms, and the latency of the cervical C2 potential (the major cervical potential) and cortical N1 (thought to be the first response of the primary somatosensory cortex). The comparative normal values were taken from our own study of 40 normal term infants.[13]

All the surviving infants were followed up and assessed at one year of age. This assessment was done by an investigator (MG) unaware of the SEP results or the extent of the encephalopathy. One infant was assessed by his local paediatrician. The other 19 infants were seen in their own homes and had a Griffiths' assessment[14] and a neurological examination performed. The data available, therefore, were the Griffiths' subscale scores the Griffiths' quotient (GQ) and the neurological findings.

DEFINITIONS

In our study of normal term infants[13] we showed that there was marked variation in both waveform and latency within the range of postmenstrual age 37 to 43 weeks. A strong positive correlation was found between increasing complexity of waveform with shortening of latencies and increasing postmenstrual age. The mean (SD) cervical potentials showed little variability with C2 latency 10·1 (0·7) ms. The N1 for the whole group was 30·1 (6·8) but much less widely scattered data were obtained within each of the four waveforms encountered. It was decided to base a decision of abnormality on the appropriateness for the infant's postmenstrual age of the measured waveform and the latency of the measured N1 for that waveform. The upper limit of normal latency was taken as the mean plus 3 SD because the control data on normal infants were slightly skewed to the left. We found on repeated runs that normal immature infants may initially have absent cortical potentials that are uncovered by an increase in stimulus intensity or decrease in stimulus frequency and hence the manoeuvres described above were employed to attempt to uncover a waveform when the initial runs showed no potentials.

In the present study of asphyxiated infants the results obtained from cortical electrodes in each individual recording session could then be split into three main groups. (1) *Normal*: responses appropriate in both latency and waveform for the infant's postmenstrual age. (2) *Abnormal*: measurable response with either delayed N1 (>+3 SD from mean) for the encountered (appropriate) waveform or inappropriately immature waveform with normal N1 latency for that form. (3) *Flat*: complete absence of identifiable response—that is, flat traces on repeated runs.

Results

SEP

A total of 111 studies were performed on the 30 infants giving a mean of 3·7 and a mode of three studies. Three infants had only one study before death and the largest number in any one infant was 10 studies. Eighteen infants were studied on day 1, seven were first studied on day 2, four first studied on day 3, and one on day 7. Cervical SEP were easily measured in all but one infant who was studied only a few hours before death, revealing no measurable potentials. In the other 29 infants cervical potentials were always normal even in those infants who had suffered shoulder dystocia during delivery (two infants).

The usual pattern over the course of the encephalopathy was for a progression of results from abnormality to normality. Asymmetry of response did occur but was seldom marked except in infant 20 (see below). Eleven infants had persistently normal SEP throughout their encephalopathy (pattern A). In addition, a further two infants had abnormal SEP with delayed latency of N1 in the first two days but normal SEP results thereafter (pattern B). Nine infants had initial potentials which were absent or severely abnormal and then the potentials were abnormal or absent for a variable length of

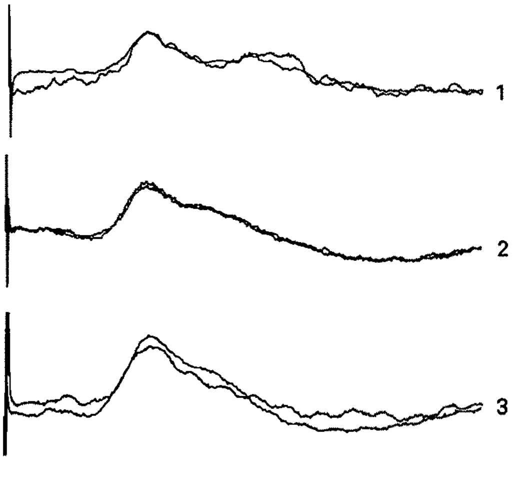

Figure 1 Infant 4 (41 weeks' gestation). Superimposed traces of response to left median nerve stimulation measured at C"4-Fpz on days 1, 2, and 3: pattern A.

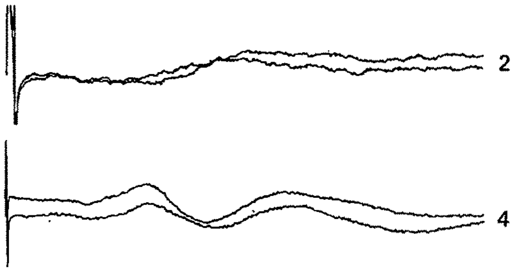

Figure 2 Infant 29 (42 weeks' gestation). Superimposed traces of response to left median nerve stimulation measured at C"4-Fpz on days 2 and 4: pattern B.

time before returning in an immature fashion in which they persisted or normalised (pattern C). In the other eight infants, all of whom had severe encephalopathy, the findings were of persistently flat traces with no cortical response measured at any time (pattern D). Examples of patterns A, B, C, and D are shown in figs 1–4.

OUTCOME

Ten of the infants in the study died. All of these infants had a pattern of neurological abnormality consistent with severe hypoxic-ischaemic encephalopathy. They died between 2 and 70 days but mostly in the first week of life.

The surviving infants were followed up to assess their outcome. One infant was seen by his local paediatrician and thought to be neurodevelopmentally normal. The results of the Griffiths' assessment subscales and GQ scores are available for 19 infants who were seen at a mean age of 12 months (range 9·5 to 14·5 months). They showed a wide range of results from 64 to 123. On neurological examination there were three infants with cerebral palsy, two of whom had spastic quadiplegia and were developmentally delayed (GQ 64 and 72) and one with a left hemiplegia (GQ 110). There were four other infants with low GQ scores (72, 85, 87, and 90) and questionable neurological findings who are best described as 'dystonic.' There are therefore three outcome groups among the survivors: unequivocal normality with normal neurology and high Griffiths' score, dystonic infants with questionable neurological findings and GQ scores in the lower part of the normal range, and those with clear abnormality manifest as cerebral palsy.

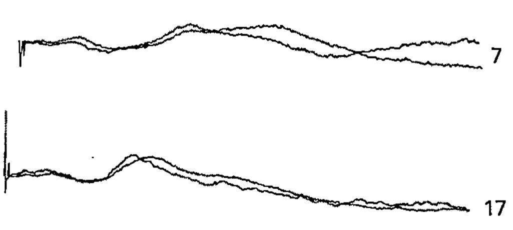

Figure 3 Infant 20 (39 weeks' gestation). Superimposed traces of response to right median nerve stimulation measured at C"3-Fpz on days 2, 4, 7, and 17: pattern C.

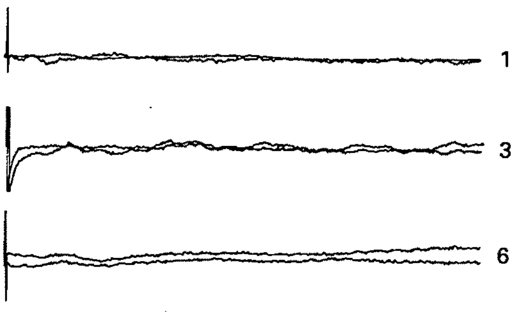

Figure 4 Infant 14 (40·5 weeks' gestation). Superimposed traces of response to right median nerve stimulation measured at C"3-Fpz on days 1, 3, and 6: pattern D.

CORRELATION OF SEP WITH OUTCOME

The relationship of outcome to encephalopathy grade is shown in table 1 and is comparable with other studies reported in the literature. Table 2 shows the relationship of outcome to SEP pattern. The infants' outcome results were divided into normal outcome (13 infants), which was unequivocal neurological normality with normal GQ score, and abnormal outcome (seven infants) which includes the three infants with cerebral palsy and four in the dystonic group. The serial SEP results of those whose SEP changed over the course of their encephalopathy are shown in table 3. Those that had a normal outcome had reached normal SEP results by 4 days of age. All seven of the infants in the abnormal outcome group had abnormal SEP studies persisting beyond 4 days. There was no clear difference between those with cerebral palsy and the dystonic infants in terms of length of persistence of SEP abnormality nor of its pattern.

Of the 10 infants who died, eight had absent cortical SEP on all occasions. The infant who died of spinal muscular atrophy had normal cortical potentials. The other infant who died of cardiovascular complications of his asphyxia (infant 15) had bilaterally abnormal potentials at day 5 and then persisting asymmetry thereafter. Therefore no infant dying of asphyxia had normal potentials by 4 days.

Discussion

From the literature there are a number of investigations which can assign a good prognosis to an asphyxiated infant. These are the presence of only grade one hypoxic-ischaemic encephalopathy,[2 15] a normal EEG[2] or a normal computed tomogram in the second week of life.[7] It is

Table 1 Relationship of encephalopathy grade to outcome

Encephalopathy	*Outcome*				*Total*
	Normal	*Dystonic*	*Cerebral palsy*	*Died*	
Mild	8	0	0	0	8
Moderate	4	1	1	0	6
Severe	1	3	2	10	16

Table 2 Relationship of SEP pattern to outcome

SEP	*Outcome*				*Total*
	Normal	*Dystonic*	*Cerebral palsy*	*Died*	
A	10	0	0	1*	11
B	2	0	0	0	2
C	1	4	3	1	9
D	0	0	0	8	8

See text for definition of patterns
*Child with spinal muscular atrophy.

Table 3 *SEP results over the first 10 days related to those whose SEP changed (patterns B and C). Right (R) and left (L) refer to the median nerve stimulated (NI measured in ms)*

	Days								*Comments*	*Outcome*
	1	*2*	*3*	*4*	*5*	*7*	*9*	*10*		
Infant 7										
R	Absent		Absent		Absent	Immature form N1 52·4		Immature form N1 57·0	Persistent delayed or immature SEP at 6 weeks	Doubtful neurology GQ 85
L	Absent		Absent		Absent	Immature form N1 46·6		Immature form N1 39·8		
Infant 8										
R	Imature form N1 34·3		Absent		Absent	Immature form N1 34·8			Normal response at 7 weeks	Doubtful neurology GQ 88
L	Imature form N1 37·1		Absent		Absent	Immature form N1 36·2				
Infant 15										
R		Normal form N1 29·4		Delayed N1 66·8		Immature form N1 30·2	Normal form N1 27·8			Died
L		Imature form N1 44·0		Delayed N1 123·0		Normal N1 32·4	Delayed N1 38·6			
Infant 20										
R		Absent/immature N1 54·6		Delayed N1 45·4		Delayed N1 36·8			At 17 days right normal and left absent	Left hemiplegia GQ 110
L		Absent		Absent		Absent				
Infant 21										
R	Absent		Immature form N1 39·2		Absent	Absent			Response still immature at 14 days	Spastic quadriplegia GQ 72
L	Absent		Absent		Absent	Absent				
Infant 22										
R	Normal N1 31·6		Absent		Absent	Immature form N1 38·2			Normal on right, immature on left at 14 days	Spastic quadriplegia GQ 64
L	Absent		Absent		Absent	Absent				
Infant 25										
R	Absent	Delayed N1 43·2	Normal N1 33·2						Normal response when next tested at 25 days	Normal neurology, developmentally normal
L	Absent	Normal N1 29·9	Delayed N1 36·0							
Infant 26										
R	Delayed* N1 34·8			Normal N1 29·7						Normal GQ 13
L	Normal N1 34·6			Normal N1 27·8						
Infant 28										
R		Absent		Absent		Absent	Absent		Still immature/delayed at 30 days	Doubtful neurology GQ 90
L		Absent		Absent		Absent	Absent			
Infant 29										
R		Normal N1 35·1		Normal N1 30·6						Normal GQ 123
L		Delayed N1 59·2		Normal N1 29·0						
Infant 30										
R		Absent		Absent		Delayed* N1 34·6*			Still delayed at 23 days	Dystonic GQ 72
L		Absent		Delayed N1 35·2		Delayed N1 36·4				

*Mature waveform present which has mean +3 SD for N1 of 32·9.

almost as clearcut to pick out those infants at extremely high risk of abnormal neurodevelopmental outcome on the basis of an isoelectric EEG,[5] extensive hypodensity on computed tomography,[6] severe brain energy depletion shown by ^{31}P nuclear magnetic resonance spectroscopy,[16] marked abnormality of Doppler signals from assessment of cerebral blood flow velocity,[4] or profound and persisting neurological abnormality.[1] However, these investigations all leave a grey area of infants with the same test result and differing outcome. The attraction of SEP is the ability to measure an index of function in the areas of the brain most severely affected in perinatal asphyxia.

There have been two previous studies of SEP in perinatal asphyxia. Hrbek *et al* described the use of SEP and visual evoked potentials in 57 infants.[8] Their study is very difficult to assess as they do not state the gestational age of their patients, the method is not described, and there is no data on follow up. However, they developed a scoring system of SEP abnormality and reported those with the highest score (most abnormal SEP) to have the worst asphyxia. A more complete study by Willis and colleagues looked at 10 term asphyxiated infants followed up to a mean of 20 months.[9] These authors aimed to perform SEP at 2, 4, and 6 months and defined abnormality as N1 absent or more than 3 SD above the mean. Persistently normal SEP predicted normal outcome and persistently abnormal SEP predicted severe disability at follow up. Those with abnormal SEP at 2 months which improved had only moderate or mild disability at follow up. Both of these studies are supported by our data. We also found that those with the most abnormal SEP had suffered the greatest asphyxial insult but, in addition, we found that SEP can be predictive in the neonatal period.

We included data on the cervical response as the presence of a cervical response of normal form and latency shows that any abnomality of cortical response occurs as a result of dysfunction in the central part of the pathway and is not due to peripheral damage as might occur in shoulder dystocia. We did not have access to the technique of electromagnetic stimulation of the motor cortex.[17] It is motor function that is most often impaired in infants who have sustained asphyxial damage and this technique might have allowed a more specific look at the effects of perinatal asphyxia on the motor pathways during the encephalopathy. However, our hypothesis that abnormality of sensory pathway function might reflect damage in motor areas would seem reasonable.

The effects of sleep state and of drugs must be considered. The first line anticonvulsant used during our study was phenobarbitone and it has been shown to have no effect on SEP.[18 19] Sleep state is known to alter the waveform and amplitude of the short latency SEP[20 21] but not signficantly to affect the latency, which was the major characteristic we assessed. Sleep state is also altered in encephalopathic infants and any test used has to be employed in the circumstances that present.

We have previously shown that there is a wide range of normal latency for N1 in the term newborn infant.[13] We described different waveforms which became increasingly complex with increasing maturity. The abnormalities shown in the asphyxiated infants in this study are mostly profound. Criticism could be levelled at the category of abnormality relating to the inappropriateness of the form or latency for the infant's postmenstrual age. Most of the variation in N1 latency for the whole group of normal infants (SD 6·8 ms) related to a wide range of N1 in the immature waveforms (immature infants), whereas in the mature forms the SD of N1 is only 2·2 ms. It was therefore thought important to relate results to maturity of the infant as this was the main variable found in normal infants. It is of note that in the more severely asphyxiated infants when the SEP first returned it was in a form which we found associated with the least mature infants and therefore abnormal for that infant's postmenstrual age. This is consistent with findings of the recovery of EEG in sick neonates.[22] Studies in older children with coma[23–25] have shown that SEP may be lost early on but rapid recovery of SEP is associated with good outcome and sustained abnormality of SEP correlates with poor outcome. We have shown that this is also the case in perinatal asphyxia.

The only infant (number 20) with appreciable asymmetry of SEP had persisting absence of cortical response on stimulation of the left median nerve until discharge from the unit at 17 days. There was improvement over time from abnormal to normal on right median nerve stimulation. This is demonstrated in fig 3. Unfortunately he was not subsequently studied. Computed tomography in the neonatal period showed the appearances of neonatal stroke of the right hemisphere and on follow up he had a left hemiplegia.[26 27]

The timing of any neurodevelopmental assessment in a cohort of sick neonates will always have a potential effect on the results. At one year it is relatively easy to pick out those with unequivocally normal outcome and those with cerebral palsy but a grey area will inevitably remain. Later assessment allows more and more scope for profound influences from upbringing and other illness factors. Piper *et al*, using the Griffiths' assessment, in a cohort of preterm infants examined at 6, 12, and 24 months, showed that at one year 25% were neurodevelopmentally suspect but only 12% at two years.[28] Much of this change was accounted for by movement from the suspect group to frank abnormality. It is likely that some infants in our doubtful group will prove to have clearer abnormalities on later testing.

Prediction of outcome in the perinatally asphyxiated term infant can be difficult but our results suggest that SEP may have a part to play. We were able to confirm that infants with mild encephalopathy all had the same SEP results and a good outcome but that, in addition, a group of infants with moderate encephalopathy and one infant with severe encephalopathy also had the same SEP results and had a normal outcome. In our study the infants with normal potentials by 4 days of age were all neurodevelopmentally normal on follow up at 1 year of age. None of the infants with abnormal SEP beyond this time had a normal outcome.

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Blood leucocyte count in the human fetus

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Abstract

Total and differential leucocyte counts were measured in cord blood samples obtained by cordocentesis (n=316) or at elective caesarean section (n=11) from normal fetuses of between 18 and 40 weeks' gestation. The total fetal leucocyte count increased exponentially from 2·8×10⁹/l at 18 weeks to 11·8×10⁹/l at term. The lymphocyte and monocyte counts increased linearly and the number of neutrophils increased exponentially from a mean value of 0·2×10⁹/l at 18 weeks to 0·8×10⁹/l at 31 weeks and then 8·5×10⁹/l at term. Early myeloid cells, eosinophils, and basophils were observed in 24%, 55%, and 15% of the blood films respectively; they contributed less than 2% to the total leucocyte count and there were no significant changes with gestation. The physiological leucopenia observed in fetuses early in the third trimester may partly explain the predisposition of premature neonates to infection.

Knowledge of fetal blood leucocyte counts has been based largely on analysis of cord blood obtained at term or premature delivery (table 1)[1–9] and after spontaneous abortion.[10] However, the assumption that these data represent normal physiological values may not be valid as the stress of delivery or the underlying reason for spontaneous abortion or premature delivery, such as infection or hypoxia, could affect fetal haemopoiesis.

Potentially more reliable, but incomplete, data to allow delineation of changes with gestational age have been provided from the study of fetal samples obtained at hysterotomy, fetoscopy, and cordocentesis.[10–13] The present study was undertaken to establish comprehensive reference ranges for the total and differential leucocyte counts from 18 weeks' gestation to term.

Patients and methods

The fetal total and differential leucocyte counts were measured in umbilical cord blood samples obtained at cordocentesis (n=316) or at elective caesarean section (n=11) from fetuses of between 18 and 40 weeks' gestation. The study was cross sectional and in each case gestation was determined from the menstrual history or by an ultrasound scan in early pregnancy.

The indications for cordocentesis included: (i) prenatal diagnosis of inherited coagulation disorders, for example, haemophilia A (n=29), (ii) maternal rubella or toxoplasmosis infection (n=21), (iii) fetal karyotyping (n=243), and (iv) fetal blood grouping in red cell isoimmunised pregnancies (n=23). Cordocentesis was performed without maternal sedation or fetal paralysis. At the time of cordocentesis, the fetal blood gases and abdominal circumstances were normal for gestational age.[14] All fetuses included in the study were subsequently shown to have a normal karyotype, to be unaffected by the coagulation disorders or infection under investigation or, in cases of suspected red cell isoimmunisation, to be Coombs' negative.

Cord blood samples at delivery were obtained from patients undergoing elective caesarean section at 37–40 weeks' gestation for previous caesarean section (n=6) or breech presentation (n=5); all infants were normal and of appropriate size for gestation.

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Table 1 Summary of data from previous reports on total leucocyte, lymphocyte, and neutrophil counts in samples obtained from babies delivered at different gestations when samples were taken from the umbilical cord, heel, or other peripheral vessels. Also shown are data from hysterotomy, termination of pregnancy (TOP), fetoscopy, and cordocentesis studies. The values given are the means; when a range is given this represents the mean values at the lowest and highest gestation

Author	*No of infants studied*	*Gestational age (weeks)*	*Vessel sampled or sampling method*	*Age at at sampling*	*Counts (×10⁹/l)*		
					Total leucocytes	*Lymphocytes*	*Neutrophils*
Manroe *et al*[1]	434	29–40	Heel+other peripheral vessels	>120 Hours	—	—	3·6
Weinberg *et al*[2]	393	29–40	Heel+other peripheral vessels	<60 Hours	—	4·2	—
Coulombel *et al*[3]	132	27–43	Heel+cord	<12 Hours	—	—	6–12
Xanthou[4]	68	>37	Heel	<96 Hours	9·7	3·9	4·1
Washburn[5]	6	>37	Heel	<10 Days	15·2	4·2	9·9
Diaz-Jouanen *et al*[6]	12	>37	Cord	Not given	—	2·1	—
Lippman[7]	42	>37	Heel	<2 Hours	10·1	4·1	5·2
Lucas *et al*[8]	159	Not given	Peripheral vessels	<24 Hours	12·2	—	—
Rosse *et al*[9]	57	>37	Peripheral vessels	<2 Hours	11·5	3·5	6·5
Playfair *et al*[10]	137	8–27	Hysterotomy+TOP		—	≈1–10	≈0·05–10
Thomas and Yoffey[11]	36	10–25	Hysterotomy		—	≈0·4–3	≈0·05–1
Millar *et al*[12]	99	15–21	Fetoscopy		1·6–2·7	1·4–2·3	0·1–0·2
Forestier *et al*[13]	163	18–30	Cordocentesis		4·2–4·4	3·3–3·6	0·2–0·4

Fetal blood samples (180 µl) were collected into 20 µl of isotonic edetic acid solution (0·5 mmol/l in 0·15 mmol/l sodium chloride). Maternal contamination was excluded by the acid elution (Kleihauer) method. The total nucleated cell count was determined with a Coulter Stacker Automated Cytometer (Coulter Electronics). Blood films were stained by the May-Grünwald-Giemsa method and after adjustments for the presence of the nucleated red cells (erythroblasts), the differential leucocytes were determined by morphological classification of 100 cells.

STATISTICAL ANALYSIS

Regression analysis was used to derive reference ranges (mean, 5th, and 95th centiles) for the total and differential leucocyte counts with gestation. Normality of the distribution of residuals was examined using the Shapiro-Francia W' test.[15] Where the distribution of the residuals was skewed, logarithmic transformation was used to achieve a normal distribution. To produce the reference ranges with gestation in the original units, the limits of the calculated reference range in logarithmic units were subjected to an antilogarithmic transformation.

Results

The total leucocyte count in the fetus increased exponentially with gestation from a mean of $2{\cdot}27\times10^9$/l at 18 weeks to $9{\cdot}41\times10^9$/l at 40 weeks (fig 1). This increase reflected two components, a linear increase in the lymphocyte count from a mean of $1{\cdot}17\times10^9$/l at 18 weeks' gestation to $3{\cdot}67\times10^9$/l at 40 weeks (figs 2, 3), together with an exponential rise in neutrophil numbers from a mean value of $0{\cdot}77\times10^9$/l at 31 weeks to $8{\cdot}53\times10^9$/l at 40 weeks (figs 2, 3).

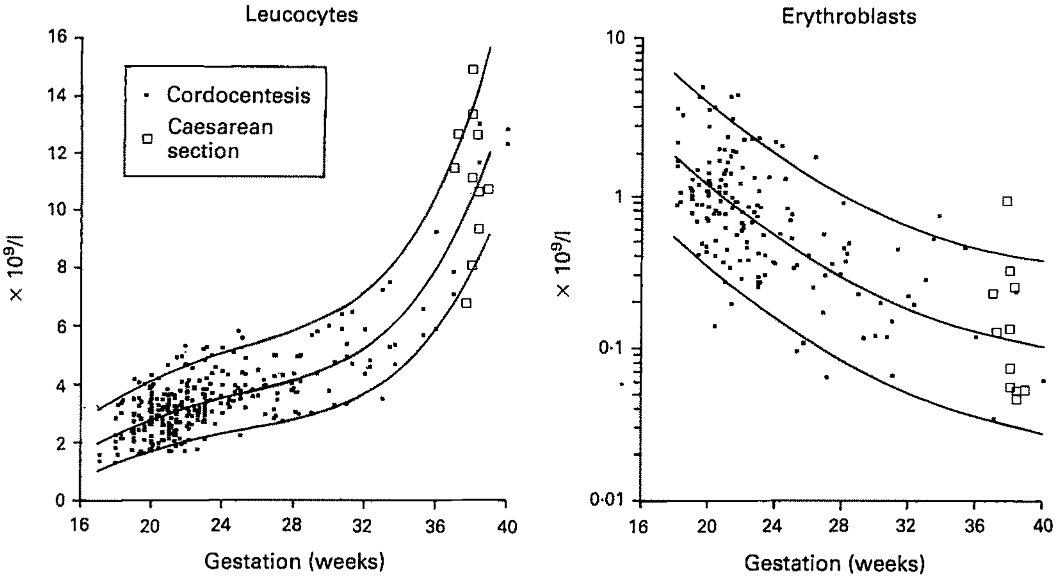

Figure 1 Reference range (mean, 5th, and 95th centile) for total fetal leucocyte (×10⁹/l) and erythroblast (×10⁹/l) counts with gestation derived from the study of umbilical cord blood samples obtained by cordocentesis or at elective caesarean section.

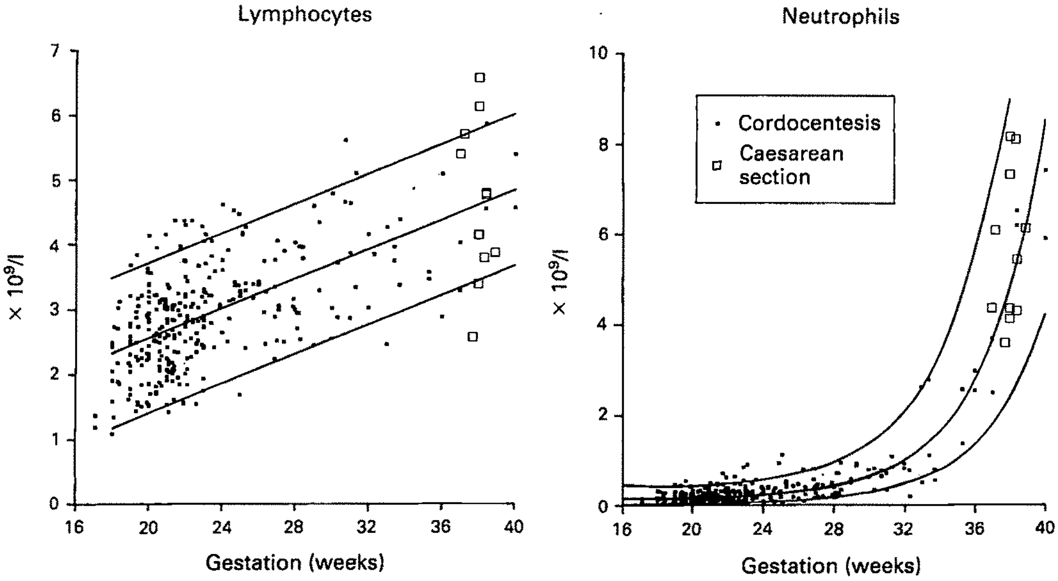

Figure 2 Reference range (mean, 5th, and 95th centile) for the number (×10⁹/l) of fetal lymphocytes and neutrophils with gestation derived from the study of umbilical cord blood samples obtained by cordocentesis or at elective caesarean section.

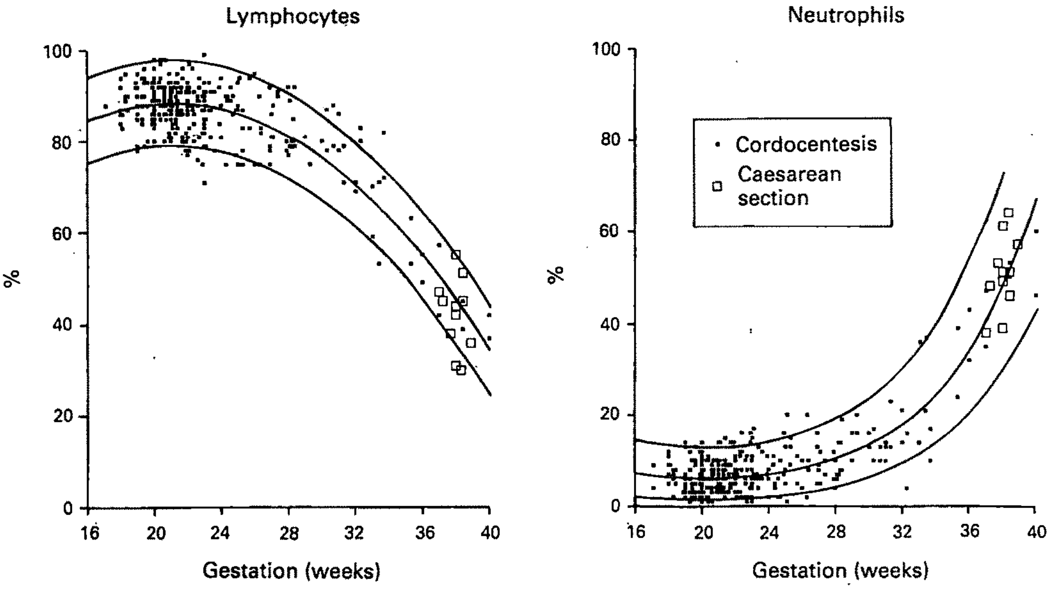

Figure 3 Reference range (mean, 5th, and 95th centile) for the percentage of fetal lymphocytes and neutrophils with gestation derived from the study of umbilical cord blood samples obtained by cordocentesis or at elective caesarean section.

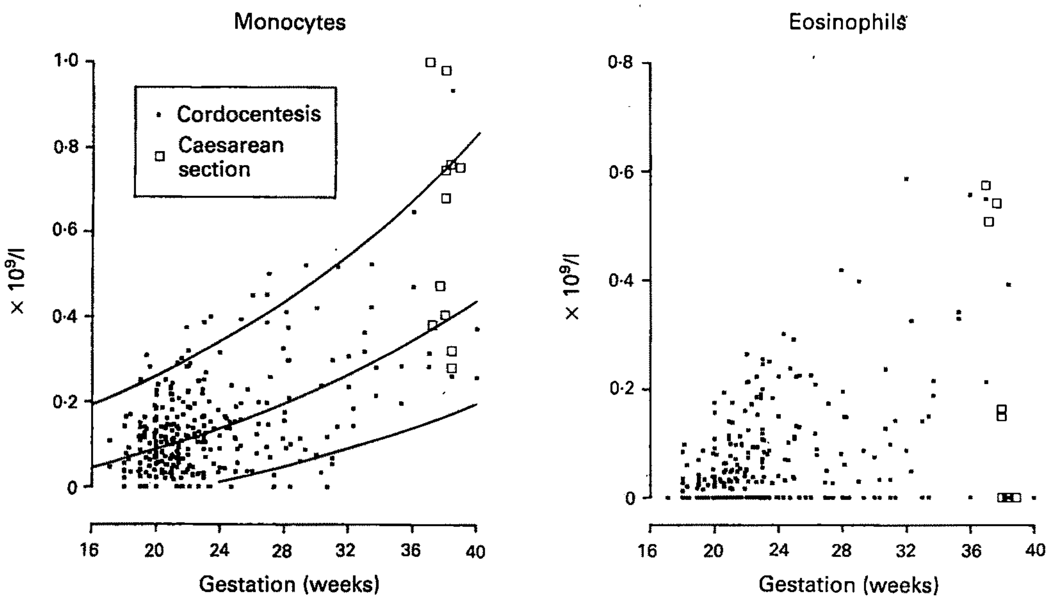

Figure 4 The number ($\times 10^9$/l) of fetal monocytes and eosinophils with gsetation in umbilical cord blood samples obtained by cordocentesis or at elective caesarean section.

Table 2 Reference ranges (mean, 5th, and 95th centile) for fetal total leucocyte, lymphocyte, neutrophil, and monocyte counts ($\times 10^9$/l) with gestational age

Gestational age (weeks)	*Total leucocytes*			*Lymphocytes*			*Neutrophils*			*Monocytes*		
	Mean	*5th*	*95th*	*Mean*	*5th*	*95th*	*Mean*	*5th*	*95th*	*Mean*	*5th*	*95th*
18	2·75	1·45	4·21	2·33	1·17	3·49	0·16	0·03	0·41	0·07	0·00	0·23
19	2·79	1·49	4·25	2·44	1·28	3·60	0·16	0·03	0·41	0·08	0·00	0·24
20	2·86	1·55	4·32	2·56	1·40	3·72	0·16	0·03	0·42	0·09	0·00	0·26
21	2·95	1·63	4·43	2·67	1·51	3·83	0·17	0·04	0·44	0·10	0·00	0·28
22	3·06	1·74	4·56	2·79	1·63	3·95	0·19	0·04	0·47	0·11	0·00	0·30
23	3·21	1·86	4·72	2·90	1·74	4·06	0·21	0·05	0·50	0·13	0·00	0·32
24	3·38	2·02	4·92	3·02	1·86	4·17	0·23	0·07	0·55	0·14	0·01	0·34
25	3·59	2·20	5·15	3·13	1·97	4·29	0·26	0·08	0·62	0·15	0·02	0·36
26	3·82	2·41	5·41	3·24	2·09	4·40	0·31	0·10	0·70	0·17	0·03	0·39
27	4·09	2·64	5·71	3·36	2·20	4·52	0·36	0·13	0·80	0·18	0·04	0·41
28	4·39	2·91	6·05	3·47	2·31	4·63	0·43	0·17	0·94	0·20	0·05	0·43
29	4·72	3·21	6·43	3·59	2·43	4·74	0·52	0·21	1·11	0·21	0·06	0·46
30	5·10	3·54	6·85	3·70	2·54	4·86	0·63	0·27	1·33	0·23	0·07	0·49
31	5·52	3·91	7·32	3·82	2·66	4·98	0·77	0·34	1·61	0·25	0·08	0·52
32	6·00	4·32	7·84	3·93	2·77	5·09	0·97	0·42	1·98	0·27	0·09	0·55
33	6·49	4·77	8·41	4·05	2·88	5·21	1·22	0·57	2·47	0·28	0·10	0·58
34	7·05	5·27	9·05	4·16	3·00	5·33	1·55	0·74	3·12	0·30	0·11	0·61
35	7·67	5·82	9·74	4·27	3·11	5·44	1·99	0·97	4·00	0·32	0·13	0·64
36	8·34	6·41	10·51	4·39	3·22	5·56	2·60	1·28	5·19	0·35	0·14	0·68
37	9·09	7·07	11·36	4·50	3·33	5·67	3·43	1·70	6·83	0·37	0·15	0·71
38	9·90	7·78	12·29	4·61	3·45	5·79	4·59	2·28	9·14	0·39	0·17	0·75
39	10·80	8·56	13·32	4·73	3·56	5·91	6·23	3·09	12·40	0·41	0·18	0·79
40	11·78	9·41	14·58	4·84	3·67	6·02	8·53	4·23	17·09	0·44	0·20	0·83

Table 3 Equations for reference ranges describing normal physiological changes in total leucocyte, erythroblast, lymphocyte, neutrophil, and monocyte counts as well as the percentage contribution of lymphocytes and neutrophils derived from measurements in 327 normal fetuses. For all parameters the normal mean for gestation=intercept+a×gestation+b×gestation^2+c×gestation^3

Parameter	*Intercept*	*a*	*b*	*c*	*SD*	*Correlation coefficient*
$\log_{10}$ (total leucocyte count+3)	−0·97	0·19	-7×10^{3}	9×10^{5}	$0·93\times10^9$/l	0·86**
$\log_{10}$ (erythroblast count)	2·67	−0·17	2×10^{3}		$1·02\times10^9$/l	0·70*
Lymphocyte count	0·27	0·11			$0·70\times10^9$/l	0·64**
$\log_{10}$ (9×neutrophil count+1)	1·44	−0·12	3×10^{3}		$0·45\times10^9$/l	0·87*
$\log_{10}$ (5×monocyte count+1)	−0·19	0·02			$0·12\times10^9$/l	0·58**
Lymphocytes (%)	21·75	6·35	0·15		5·66	0·89**
$\log_{10}$ (% neutrophils+9)	1·92	−0·07	2×10^{3}		4·52	0·82**

*$p<0·001$; **$p<0·0001$.

These changes were paralleled by a reciprocal decrease in the erythroblast count (fig 1).

Monocytes were observed in the majority of samples, irrespective of gestational age. Their numbers increased linearly with gestation, from a mean of $0·07\times10^9$/l at 18 weeks to $0·44\times10^9$/l at 40 weeks (fig 4). Eosinophils were present in 55% of samples and there was a non-significant increase in the total number with gestation (fig 4).

Early myeloid cells (metamyelocytes, myelocytes, promyelocytes, and blasts) and basophils were observed in 24% and 15% of the blood films respectively. They contributed less than 2% to the total white count and there was no significant change with gestational age. Reference ranges for the total and differential leucocyte counts at different gestational ages between 18 and 40 weeks are shown in table 2. Equations describing the observed changes with gestation in the total leycocyte, lymphocyte, neutrophil, and monocyte counts are summarised in table 3.

Discussion

In normal human pregnancy the fetal leucocyte count increases with gestational age. Until 37–38 weeks' gestation lymphocytes predominate. However, from 32 weeks onwards the proportion of neutrophils increases to become the commonest leucocyte at term.

In the second trimester, the total and differential leucocyte values observed in this study concur with those found in fetal blood obtained at hysterotomy and fetoscopy,[10–12] but they are lower than those observed after spontaneous abortion.[10] This may reflect the effects on leucopoiesis of those factors underlying spontaneous abortion or the process of abortion itself. The observed progressive rise in the fetal leucocyte count contradicts the reported absence of a significant change from 18 to 30 weeks' gestation in a previous study, which also examined samples obtained by cordocentesis.[13] The most likely explanation for this discrepancy is that in the study of Forestier *et al* no adjustments were made for the presence of nucleated red blood cells.[13]

In the third trimester, the leucocytes count was lower than that reported in studies which examined cord blood after preterm or term delivery.[1–9] These findings suggest that either delivery itself and/or the causes of preterm delivery affect the number of circulating leucocytes. Additionally, the majority of neonatal studies have utilised heel prick capillary samples, which yield values approximately 20% higher than those obtained from a vein or artery.[16]

The observed changes in the number of circulating leucocytes as well as changes in other fetal haematological values with gestation[17 18] presumably reflect alterations in the pattern of differentiation of pluripotent haemopoietic stem cells to meet changing fetal physiological priorities during gestation. The first primitive oxygen carrying cells in the human fetus appear around day 14 in the yolk sac, and throughout the hepatic phase of haemopoiesis the majority of haemopoietic cells are erythroid.[19 20] The increase in lymphocyte number in mid-gestation may be reconciled with the need to acquire immunological tolerance and antigen recognition functions that are demonstrable by 20 weeks.[21] This is of potential importance in relation to viral infections, which can be placentally transmitted. In contrast, the placenta acts as an effective barrier to most bacteria,[22] and therefore the acquisition of host defence mechanisms directed against bacterial infection is only necessary in preparation for extrauterine life. This may explain the dramatic rise in the number of circulating neutrophils during the late third trimester.

The factors that regulate the alterations in the pattern of differentiation of pluripotent haemopoietic stem cells are uncertain. Although hepatic haemopoiesis is primarily erythroid,[20] fetal liver haemopoietic stem cells are capable of reconstituting all haemopoietic lineages in primates.[23] Moreover, both pluripotent and committed haemopoietic progenitors are plentiful in cultures from human fetal liver.[24] One explanation for the predominance of erythroid activity in the hepatic phase of fetal haemopoiesis may be the influence of locally produced erythrogenic growth factors such as erythropoietin.[25] Similarly, the production of leucopoietic colony stimulating factors by marrow stromal cells may partly explain the expansion in fetal leucopoiesis, which follows the switch from liver to marrow haemopoiesis.[26 27]

The findings of this study suggest that one factor responsible for the vulnerability of premature neonates to bacterial infection,[28] which is a significant cause of perinatal mortality[29] and morbidity,[30] is physiological neutropenia. In patients receiving myelosuppressive drugs or radiotherapy the risk of infection is directly related to the degree of neutropenia.[31] Leucocyte values in neonates should be interpreted in the light of in utero values at the corresponding gestational age. A clearer understanding of the mechanisms mediating leucocyte maturation in the fetus, which may include specific haemopoietic growth factors, could provide a basis for therapeutic manipulation in utero that was aimed at the prevention of bacterial infection in premature neonates.

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Fetal leucocyte count in rhesus disease

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Abstract

The effect of fetal anaemia on the total and differential leucocyte counts was studied by examining blood samples obtained by cordocentesis from 177 previously untransfused rhesus affected fetuses at 17–36 weeks' gestation. The mean fetal total leucocyte, lymphocyte, and monocyte counts were significantly lower than the corresponding values in normal controls and there were significant associations between the decrease in these cells and the degree of fetal anaemia. Possible mechanisms for leucopenia include (i) stimulation of erythroid progenitor production at the expense of production of myeloid progenitors, (ii) non-specific haemophagocytosis, or (iii) general suppression of haemopoiesis. Further understanding of the underlying mechanism and the implications of leucopenia as well as the previously reported thrombocytopenia and anaemia may provide a basis for improved antenatal and/or postnatal treatment.

In red cell isoimmunised pregnancies the life span of fetal erythrocytes is reduced because antibody coated red cells are destroyed in the fetal reticuloendothelial system. In mild-moderate anaemia there is associated reticulocytosis suggesting a compensatory increase in intramedullary erythropoiesis.[1] With severe anaemia there is recruitment of extramedullary erythropoietic sites resulting in macrocytosis and erythroblastaemia.[1 2] In mild-moderate anaemia there is associated thrombocytosis and in severe anaemia there is thrombocytopenia.[3]

The aim of the present study was to examine the effect of anaemia due to rhesus isoimmunisation on the total and differential leucocyte counts.

Patients and methods

The total and differential fetal leucocyte counts were determined in a cross sectional study of 177 previously untransfused fetuses from rhesus isoimmunised pregnancies at 17–36 weeks' gestation.

Gestation was determined from the menstrual history or an ultrasound scan performed in early pregnancy. In 32 cases ultrasound evidence of fetal hydrops (skin oedema, ascites, pleural or pericardial effusions) was found. Umbilical cord blood samples were obtained by cordocentesis, which was performed without maternal sedation or fetal paralysis.[4]

Fetal blood (180 µl) was collected into 20 µl of isotonic edetic acid solution (0·5 mmol/l in 0·15 mmol/l of sodium chloride). The full blood count was determined on a Coulter Stacker Automated Cytometer (Coulter Electronics). Blood films were stained with May-Grünwald-Giemsa on an automatic processing machine and the nucleated red blood cell (NRBC) count

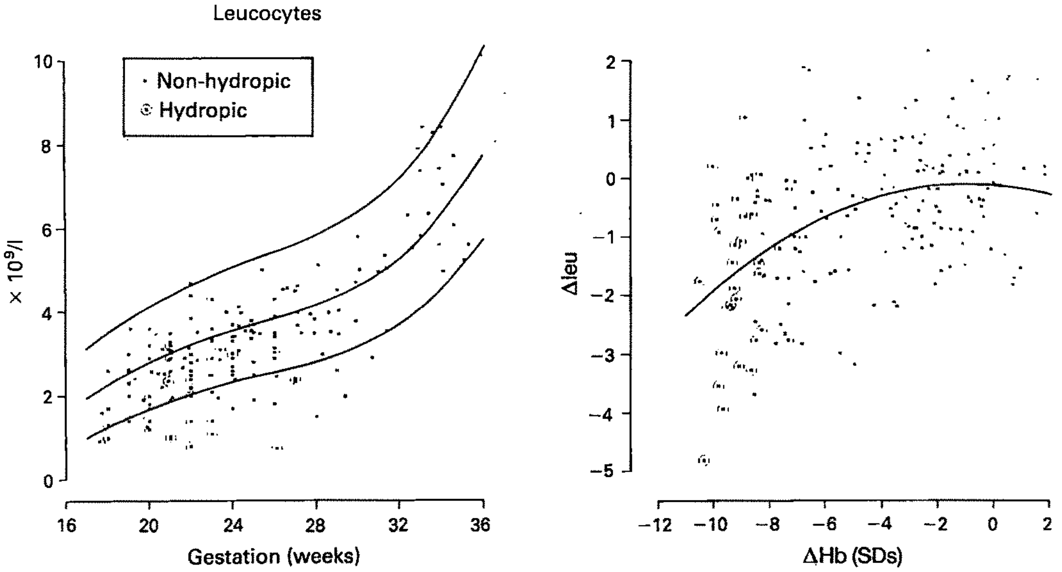

Figure 1 Total fetal blood leucocyte count in 145 non-hydropic and 32 hydropic fetuses from red cell isoimmunised pregnancies plotted on the reference range (mean, 5th, and 95th centiles) for gestation. There is a significant association between the degree of fetal leucopenia (Δleu) and anaemia (ΔHb); Δ values represent differences from the appropriate normal mean for gestation in SDs.

per 100 leucocytes was determined. The corrected leucocyte count was calculated (leucocyte count=uncorrected leucocyte count×100/NRBC count+100). To determine the differential count, 100 leucocytes were examined and classified. Kleihauer testing confirmed that all samples were fetal. Furthermore, in all cases used for this study the Coombs' test was positive.

In normal pregnancy the fetal haemoglobin concentration, platelet, and total and differential leucocyte counts change with gestation.[3 5 6] The values obtained from the rhesus isoimmunised pregnancies were expressed as the number of standard deviations (SDs) by which the individual values differed from the normal mean for gestation (Δ value). Two tailed Student's *t* test was applied to determine if there were significant differences between the findings in rhesus affected pregnancies and normals. Regression analysis was applied to determine the significance of any associations between Δ values for the individual parameters.

Results

In the rhesus affected pregnancies the mean fetal total leucocyte, lymphocyte, and monocyte counts were significantly lower than the corresponding values in normal controls.[6] This is shown in figs 1–3; mean (SEM) difference= −0·637 (0·09) SDs, t=−6·81, p<0·0001; mean difference=−0·687 (0·08) SDs, t=−8·3, p<0·0001; and mean difference=−0·536 (0·08) SDs, t=−6·77, p<0·0001 respectively. There

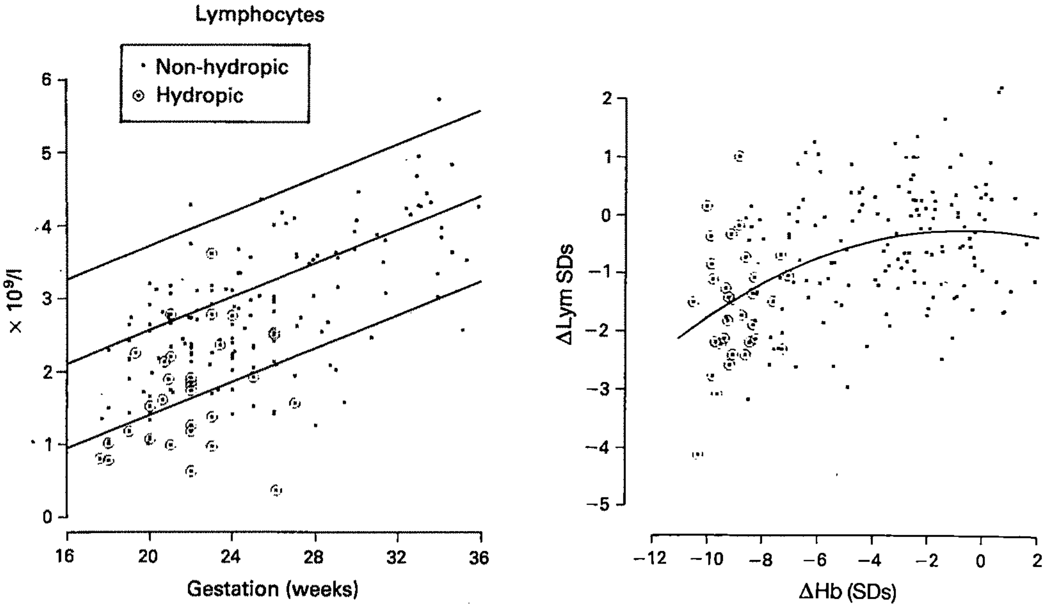

Figure 2 Fetal blood lymphocyte count in 145 non-hydropic and 32 hydropic fetuses from red cell isoimmunised pregnancies plotted on the reference range (mean, 5th, and 95th centiles) for gestation. There is a significant association between the degree of fetal lymphocytopenia (ΔLym) and anaemia (ΔHb); Δ values represent differences from the appropriate normal mean for gestation in SDs.

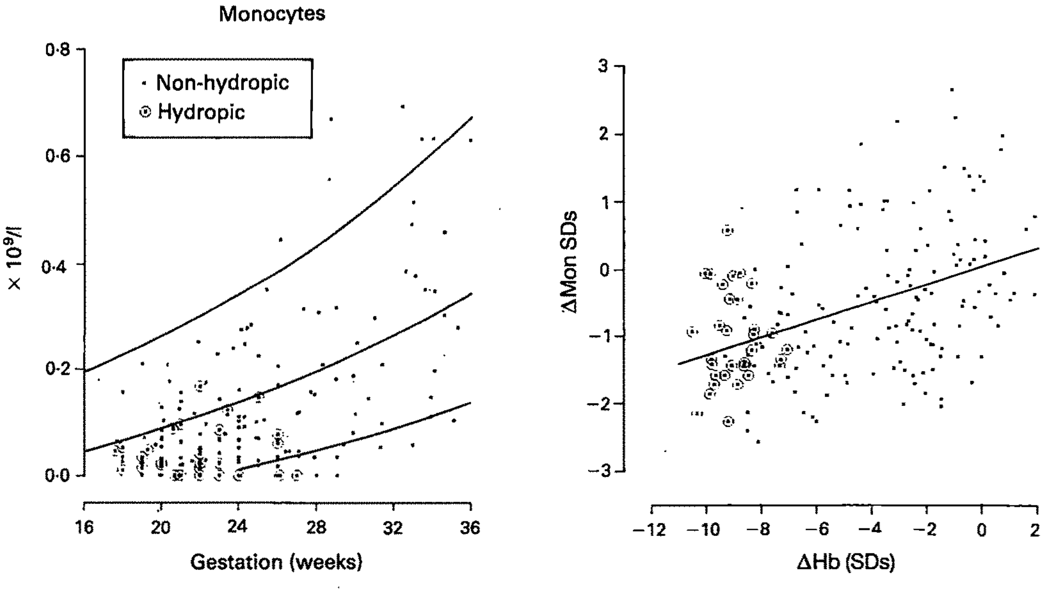

Figure 3 Fetal blood monocyte count in 145 non-hydropic and 32 hydropic fetuses from red cell isoimmunised pregnancies plotted on the reference range (mean, 5th, and 95th centiles) for gestation. There is a significant association between the degree of fetal monocytopenia (ΔMon) and anaemia (ΔHb); Δ values represent differences from the appropriate normal mean for gestation in SDs.

were no significant differences in mean neutrophil (mean difference=0·112 (0·09) SDs, t=1·19) or eosinophil counts (mean difference= 0·025 (0·02)×10^9/l, t=1·68).

There was a significant association between Δ total leucocyte count and Δ haemoglobin concentration which was best described by a quadratic equation (fig 1; r=0·470, p<0·0001). Multiple regression analysis showed that hydrops did not have a significant independent contribution to this association (F to remove hydrops=2·93, p=0·09). Similarly, there was a significant quadratic association between Δ lymphocyte count and Δ haemoglobin concentration (fig 2; r=0·439, p<0·05). There was a significant linear association between Δ monocyte count and Δ haemoglobin concentration (fig 3; r=0·413, p<0·0001).

Discussion

In rhesus isoimmunisation fetal haemolysis is associated with leucopenia. Lymphocyte and monocyte counts decreased in proportion to the degree of fetal anaemia, although neutrophil numbers appeared to be unaffected. Koenig and Christensen, using blood samples obtained postnatally from infants of rhesus affected pregnancies, also reported an association between leucopenia and severe aneamia.[7] However, their findings suggested that the infants were neutropenic. A possible explanation for this apparent discrepancy is that in intrauterine life, especially before 32 weeks' gestation, neutrophil counts are normally quite low (1–3 per 100 white cells) making it difficult to demonstrate a significant reduction.[6]

Haemopoiesis defines the production of functionally distinct mature blood cells from a common pluripotent progenitor. It is possible that in severe anaemia due to rhesus isoimmunisation the observed leucopenia, as well as the previously described thrombocytopenia,[3] may reflect the coordinated differentiation of erythroid progenitors at the expense of myeloid and megakaryocytic maturation. Although such 'channelling' of haemopoietic reserve is not commonly observed in postnatal haemolysis, Koenig and Christensen have reported that in some neonates with severe red cell isoimmunisation there is an increase in the number of erythroid progenitors accompanied by a reduction in numbers of granulocyte-macrophage progenitors.[7] Furthermore, addition of erythropoietin to cultures of human fetal progenitors reduces the number of granulocyte-macrophage colonies formed in response to granulocyte-macrophage colony stimulating factor.[8]

A further possible explanation for leucopenia and thrombocytopenia in red cell isoimmunisation is non-specific haemophagocytosis due to activation of the reticuloendothelial system.[9] This process has been observed in autoimmune haemolytic anaemia.[10] Although the phenomenon was thought to be rare, Suster *et al* have recently examined 230 consecutive adult necropsies and found evidence of moderate to severe haemophagocytosis in the bone marrow of 102 cases.[11]

In those cases where leucopenia and thrombocytopenia are associated with absence of an erythroid response, marrow suppression due to tissue hypoxia and lactic acidosis may be important.[12 13] Additionally, as in postnatal life, severe haemolysis and consequent increased erythropoietic activity could result in relative deficiency of haematinics such as folate.[14]

In summary, this study demosntrates that in rhesus affected fetuses severe anaemia is not only accompanied by thrombocytopenia but also by leucopenia. Possible mechanisms causing the reduced numbers of white cells and platelets include (i) stimulation of erythroid progenitor production at the expense of production of myeloid and megakaryocyte progenitors, (ii) non-specific haemophagocytosis, or (iii) general suppression of haemopoiesis. Further studies on the underlying mechanism and the implications of presence of leucopenia as well as thrombocytopenia and anaemia may provide a basis for improved antenatal and/or postnatal treatment.

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Plethysmographic validation of near infrared spectroscopic monitoring of cerebral blood volume

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Abstract

The validation of measurement of cerebral blood volume (CBV) and cerebral blood flow (CBF) using near infrared spectroscopy (NIRS) against jugular venous occlusion plethysmography is described. Repeated measurements in six infants were made using both techniques simultaneously. A close relationship between the two measurements of change in CBV was obtained in five infants. There was also a close relationship for measurement of CBF in four infants. This study confirms the possibility of using NIRS to monitor CBV continuously in the premature infant. This parameter may prove to be of greater clinical value than the intermittent measurement of CBF.

Near infrared spectroscopy (NIRS) is a new technique originally proposed by Jobsis in 1977 for continuous monitoring of cerebral haemoglobin concentration and oxygenation.[1] The NIRS instrumentation developed in this department has been used to study these cerebral parameters continuously by transillumination of the neonatal head. Algorithms are used to convert the changes in absorbance at individual wavelengths to changes in the concentration of oxygenated, deoxygenated, and total haemoglobin.[2] Assuming a constant packed cell volume, a changed in total haemoglobin implies a change in cerebral blood volume (CBV). Clinical studies using this technique have demonstrated that, whereas mild hypoxaemia leads to an increase in CBV, bradycardia causes a rapid fall with a small overshoot on recovery.[3] Changes in CBV attributable to alterations in carbon dioxide tension have also been documented.[4 5] Although the magnitude of these changes can be calculated from theoretical considerations, the technique for measurement of CBV has never been validated by an independent technique.

Strain gauge plethysmography has been used to calculate cerebral blood flow (CBF) from a consideration of change in cerebral volume in relation to time.[6] Although the technique has been criticised for this purpose, it is generally accepted that an accurate measurement of increase in head circumference resulting from jugular venous occlusion does provide a useful method of quantifying volume change.

Methods

INSTRUMENTATION

NIRS

This technique uses near infrared light emitted by three semiconductor laser diodes to transilluminate the neonatal head.[7–9] The near infrared light from the semiconductor diodes is coupled to an optical fibre, which is attached to the head. The light emerging after absorption is collected by a similar optical fibre bundle, detected by an avalanche photodiode and amplified. After initial calibration, the overall absorbance at each of the three wavelengths (775 nm, 845 nm, and 904 nm) can be determined. The principle behind the technique is that the absorbance at these wavelengths is sensitive to the concentrations of oxygenated and deoxygenated haemoglobin in the brain.

For the analysis a modified form of Lambert-Beer law is assumed to hold for biological tissue. In its simplest form this may be expressed as:

$$A=eCnL+B$$

where, A is the optical absorption (optical density units) of the chromophore of concentration C (mmol/l) having an absorption coefficient e (l/cm×mmol) and a physical path length L (cm); and B is a term to account for the losses in absorption due to the skin–probe interface and scattering. The optical path length is expressed as nL where n is a path length multiplication factor used to take into account the increase in optical pathlength due to scattering, and we have used a factor of 4·3.[4]

Thus change in absorbance can be related to change in concentration as:

$$\Delta A=\Delta C(enL)$$

provided the assumption is made that scattering and losses at the skin–fibre interface remains unchanged during the study period.

Thus if ΔA_{775}, ΔA_{845}, and ΔA_{904} are the changes in absorbances at these wavelengths then change in total haemoglobin (HbT) is given by:

$$\Delta[\mathrm{HbT}]=[(0{\cdot}485)(\Delta A_{775})+(0{\cdot}861)(\Delta A_{845})+(1{\cdot}249)(\Delta A_{904})]/nL \text{ mmol/l}$$

where L is the direct spacing between the optical probes.

NIRS cannot be used continuously to monitor absolute CBV, but can be used to monitor changes in the total haemoglobin in the neonatal brain. The change in total haemoglobin is normally given as mmol/l but can be converted to blood volume if the packed cell volume is known, and assuming a cerebral to large vessel packed cell volume ratio of 0·7.[4] The molecular weight of haemoglobin is taken to be 64 500. Thus the change in CBV may be expressed as ml/100 ml. The CBF can be calculated from the rate of change of blood volume as monitored by NIRS, and expressed as ml/100 ml/min.

Strain gauge plethysmography

Strain gauge plethysmography employs a Wheatstone bridge to determine the changes in length of the gauge.[10] [11] This technique can be adapted to determine CBF.[12] [13] For neonatal cerebral studies the strain gauge consists of a silicone rubber tube of internal diameter 1 mm and length 50 cm which is filled with mercury. The tube is doubled on itself to form a four stranded gauge. Copper pins are attached to the ends for electrical connections, and connected to one arm of the bridge circuit.

The electronic circuit produces a voltage change which is proportional to the change in occipitofrontal head circumference of the baby, when the jugular veins are occluded. The near infrared data and strain gauge information can be displayed and stored simultaneously.

The technique relies on the compliance of the neonatal skull due to the softness of the bones and lack of fusion of the sutures. It is assumed that any change in CBV causes the entire head to expand or contract isotropically. The change in head circumference when the overall length of the gauge is changed by 1 mm can be determined in situ with the calibration device. Provided the head circumference is known, the change in CBV as a result of jugular venous occlusion can be calculated as given below. The rate of change of CBV can also be calculated to give a measure of apparent CBF. This acknowledges the assumptions inherent in the technique, which tend to lead to an underestimate of flow.[6]

Cooke *et al* have reported that the relationship between brain weight and occipitofrontal head circumference is cubic in nature[12]:

$$\text{Brain weight}=C^{3\cdot001}\times0\cdot009$$

where C is the occipitofrontal circumference. As the relationship between brain weight and volume (V) is linear, and also assuming that the density of brain is 1·06, the brain volume is given by:

$$V=C^3\times0\cdot009/1\cdot06=0\cdot0085\times C^3$$

For a small change in blood volume:

$$dV=3\times0\cdot0085\times C^2dC=0\cdot0255\times C^2dC$$

Apparent CBF is determined as the rate of change of blood volume, and is given by:

$$dV/dt=(3\times V\times60/C)\times dC/dt\ \text{ml/min}$$

For 100 ml of brain tissue:

$$\text{Apparent CBF}=(3\times100\times60/C)\times dC/dt\ \text{ml/100 ml/min.}$$

Hence the slope of the blood volume change (dC/dt) provides a means of determining the apparent CBF.

PATIENTS AND PROCEDURES

Six premature infants were studied. These were all infants who had had no major neonatal problems and had normal cranial ultrasound scans at the time of the study. Gestation ranged from 31 to 33 weeks (median 32 weeks) and birth weight from 1540 to 2010 g (median 1735 g). Age at the time of study was from 3 to 16 days, median 15 days.

The infants were studied after a feed, while at rest or in quiet sleep. The head circumference was measured, the strain gauge was then placed around the occipitofrontal circumference and fastened using Velcro tape. The NIRS probes were held in place a measured distance apart using double sided adhesive rings and elastic webbing. Great care was needed to ensure that that strapping for the NIRS probes did not touch or interfere with the strain gauge. The baby was then positioned on the lap of one investigator with the head supported by a roll of cloth. The connecting wires and the NIRS optical fibres were supported to prevent any tension.

With the equipment in position and the infant at rest, small pulsations were obtained on the strain gauge trace, due to the cardiac cycle (fig 1). These were not seen on the NIRS traces because of the two second averaging time used. Occlusions were performed as follows: the two jugular veins in the lower third of the neck were occluded simultaneously using the index fingers for a period of five seconds, then released. Once the trace had returned to baseline, the occlusion was repeated, to approximately 10 occlusions. A calibration manoeuvre was then performed. In some infants it was not possible to analyse 10 occlusions because of movement artefact, and the number ranged from five to seven occlusions per patient.

This study was approved by the local ethical committee and informed consent was obtained from parents.

Results

A typical study is shown in fig 2. This was

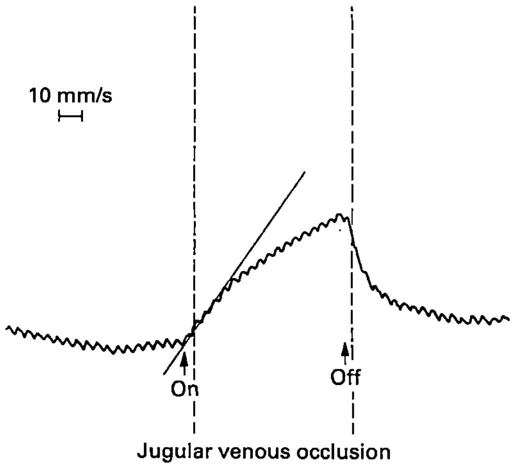

Figure 1 This shows the direct trace from strain gauge plethysmography in an infant of 32 weeks' gestation at rest. Individual cardiac pulsations can clearly be seen together with the increase in occipitofrontal circumference with jugular venous occlusion and the decrease when the occlusion is released. The oblique line indicates the slope used for calculation of apparent CBF.

carried out on an infant of 32 weeks' gestation, birth weight 1670 g, at the age of 15 days. Several jugular venous occlusions were carried out to determine the CBV and flow. The two traces showing the variations of CBV as measured by NIRS and by strain gauge can be seen to correspond.

Figure 3 shows a scatter diagram, with the line of identity, of CBV data plotted for each of the six babies. The data for five babies shows a relationship between the two methods for the magnitude of change in CBV observed during an occlusion. Results from five occlusions in one baby (baby 3) did not fit with this relationship. The mean change in CBV during a single jugular venous occlusion as measured by NIRS, excluding the data from baby 3, was 1·13 ml/100 ml, while that measured by the strain gauge techique was 1·25 ml/100 ml.

Friedman two way analysis of variance by ranks as modified by Conover[14] was carried out on the data for several observations per experimental unit. The data from baby 3 was excluded from analysis (see discussion). This analysis demands equal number of observations from each individual and therefore the first five successful occlusions from each set were used. Here the test statistic calculated is compared with χ^2 for degrees of freedom (df), k-1, where k is the number of treatment (measurement) categories (quoted figures: $\chi^2_{df=1}=3{\cdot}84$ for $p=0{\cdot}05$ and 1·32 for $p=0{\cdot}25$). The calculated test statistics for change in CBV was 0·375, which is not significant. The test demonstrates that null hypothesis appears to be valid ($p>>0{\cdot}25$) and any deviation from agreement between the methods is not significant.

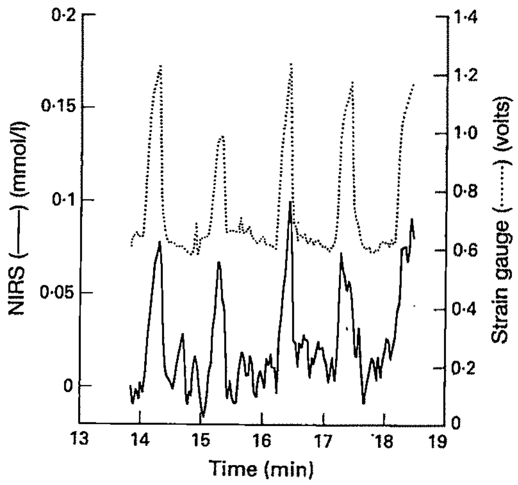

Figure 2 This demonstrates simultaneous recording of occipitofrontal circumference by strain gauge and CBV by NIRS during several jugular venous occlusions.

CBF was calculated from each occlusion using the two methods described above. The results from four babies are shown in fig 4. In the two remaining babies, CBF could not be calculated because of an artefact in the tracing. In this study low values for apparent CBF were obtained, by both methods when compared with previous published data.[15] The mean apparent CBF measured by strain gauge was 9·73 ml/100 ml/min, while the mean CBF calculated from the NIR data was 9·05 ml/100 ml/min.

Using the same statistical analysis as the CBV the calculated test statistics for CBF was 0·01, which again demonstrates that any deviation from agreement between the two methods is not significant.

Discussion

Disturbance to cerebral blood flow is likely to be an important factor in the aetiology of neonatal cerebral injury. Therefore a number of different methods have been developed for the assessment of CBF in premature infants.

The problems inherent in the technique of jugular venous occlusion plethysmography for the measurement of CBF have been described.[13]

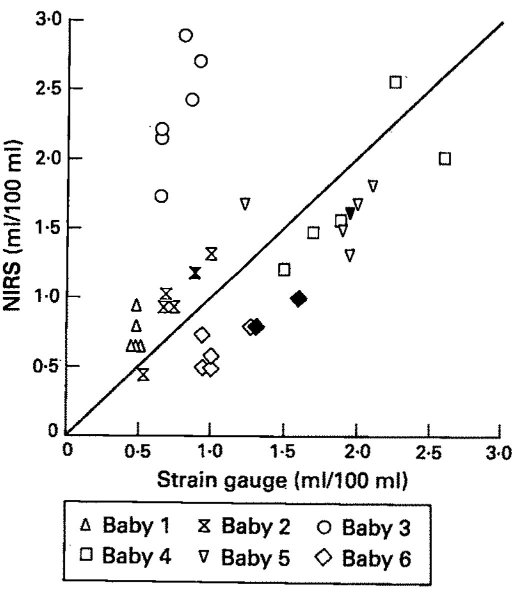

Figure 3 NIRS measurement of changes in CBV is shown plotted against strain gauge measurement for six babies individually identified. The solid symbols are data points not used in statistical analysis.

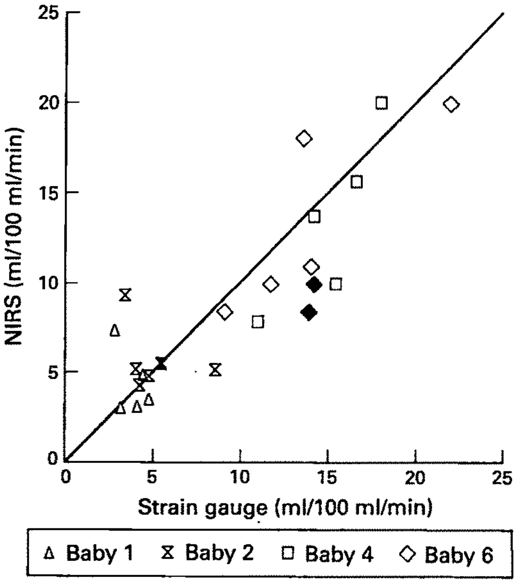

Figure 4 Data for CBF measurements by the two methods is shown for four babies (in the remaining two CBF could not be calculated). The solid symbols are data points not used in statistical analysis.

The validity of the estimation of CBF depends upon assumptions that cerebrospinal fluid is not displaced and only a small volume of blood escapes through the vertebral veins during an occlusion. The skull is assumed to be perfectly compliant. Other limitations include the practical difficulties of positioning the infant correctly and effecting a good clean occlusion. A rise in venous pressure is a necessary consequence of the technique and although this is well tolerated by healthy infants, it may be hazardous in sick infants who may already be hypoxic or hypotensive or have raised intracranial pressure. Concern has also been expressed over the use of mercury which certainly should not be used in an enclosed space such as an incubator. In summary, an estimate of global blood flow can be obtained within a few seconds, although the average of results from several jugular occlusions is required to obtain adequate precision. However, the coefficient of variation of flow by this technique has been quoted as 15% to 35%.[16]

With the exception of possible problems with skull compliance, these limitations do not apply to the use of the technique to measure changes in cerebral blood volume in healthy preterm infants. Therefore it was felt that this techique could effectively be used to validate the estimation of changes in cerebral blood volume observed using NIRS.

Examination of the raw data (fig 2) clearly demonstrates a synchronous change in occipitofrontal circumference and total haemoglobin in response to each venous occlusion. There was a close relationship between the results from the techniques for the magnitude of change observed in five infants. The infant with outlying results was larger than the others (birth weight 2010 g) and may therefore have had a less compliant skull leading to an underestimated change from the strain gauge measurement.

The change in path length which occurs during jugular venous occlusion also needs to be considered for its effect on NIRS measurements. For ease of calculation, assumption is made that the neonatal head could be approximated to a sphere with a circumference of 30 cm (fig 5). The change in occipitofrontal circumference after jugular venous occlusion lasting about six seconds is taken to be 1 mm in this example—assuming the skull to be perfectly compliant. The change in diameter for this circumferential change is from 95·45 to 95·77 mm. The optical probes for studies on neonates undergoing jugular venous occlusion are taken to be about 5 cm apart for this calculation. If it is assumed that the angle subtended is 60°, the change in physical path length is from 47·72 to 47·88 mm. This artifactual change is additive and will be reflected in the calculated haemoglobin concentration and hence will result in an overestimation of change in CBV up to 25% on babies with fully compliant skull. This error will be less on babies that have a less compliant skull.

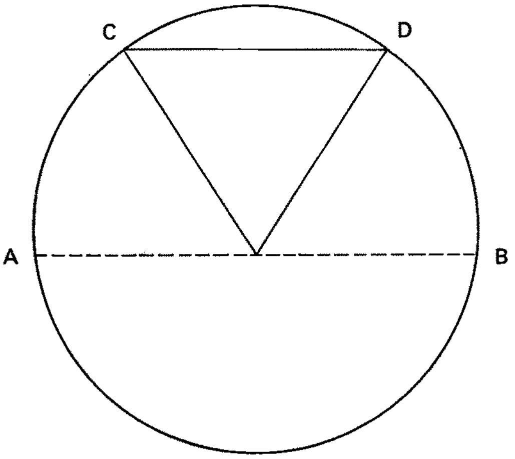

Figure 5 Change in optical path length due to jugular venous occlusion (head approximated to a sphere). AB=diameter; C and D indicate position of NIRS probes, arc length 5 cm; occipitofrontal circumference=30 cm. Angle subtended by CD at the centre is 60°.

Measurement of cerebral blood flow using NIRS gave comparable results to the strain gauge measurements. However, the limitations of using jugular venous occlusion remain. All methods of measuring CBF involve some form of intervention. A technique described by Wyatt *et al* using a small change in arterial oxygen saturation in conjunction with NIRS certainly causes less disturbance to the infant,[4] but the fact that a change is necessary means that CBF cannot be continuously monitored.

We have shown that CBV can be monitored non-invasively and continuously using NIRS. Studies using this technique have shown that measure of CBV is sensitive to changes that are known to cause changes in flow. These include bradycardia, hypoxaemia, and changes in carbon dioxide tension.[3]

If our understanding of the aetiology of cerebral ischaemic lesions occurring during intensive care is to be increased then a continuous measurement is essential. A continuous measurement of CBV may prove to be of greater value than intermittent measurements of flow.

We would like to thank the parents who gave their consent to our studies, and acknowledge the statistical consultations with Dr J Thompson and assistance of Ralph Houston and Farouk Faris in this study. The technical support given by R Bailey and T Buttery in designing the strain gauge calibration device is also acknowledged.

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Postnatal evolution of slow variability in cerebral blood flow velocity

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Abstract

The evolution of low frequency variability in cerebral blood flow velocity (CBFV) was examined in 30 consecutive admissions of very low birthweight babies. Measurement of CBFV was made on the first day of life and at weekly intervals until discharge. Altogether 133 recordings were subjected to visual classification and described as showing presence or absence of variability at a frequency between 1 and 5/minute. Amplitude of variability was expressed as the largest variation in peak systolic velocity as a percentage of the maximum systolic change.

Slow variability was usually obvious and was sometimes present for only part of the minute recorded. There was a significant trend for decreased incidence of slow variability in relation to both postconceptional and postnatal ages. Amplitude of slow variability was also damped with increasing age.

Slow variability appeared to be unrelated to the type of sedation, severity of illness, or intracranial pathology; it may be a normal phenomenon in which damping occurs as the autonomic nervous system matures.

Small variations in heart rate and blood pressure have been recognised since the nineteenth century. Traube[1] and Hering[2] described fluctuations in blood pressure at the same frequency as respiration. Mayer described waves in blood pressure slower than those of respiration in animals with spontaneous respiratory movements.[3] Guyton and Harris reported cycles of blood pressure at a frequency of 1 to 5/minute in deteriorating animal preparations.[4] Recently, Anthony *et al* have described slow variability of cerebral blood flow velocity (CBFV) in both term and preterm newborn babies at a similar frequency.[5] In short term recordings a highly variable CBFV has been implicated in the aetiology of intracranial pathology in the very low birthweight infant.[6] Slow variability is important because in a recording of CBFV lasting only part of one minute its presence might lead to misinterpretation of beat to beat variability.

In adults[7 8] and term newborn infants,[9] slow variability is thought to be influenced by both thermoregulation and by baroreceptor reflex control mediated by the autonomic nervous system, and this may also be true for the preterm infant.[10] Studies recording CBFV in adults over 30 minute periods do not report the presence of slow variablity,[11] suggesting that at some point of postconceptional age this becomes so damped as to be undetectable.

In this study we examined slow variability in CBFV in preterm infants in a longitudinal study extending to 14 weeks of postnatal age.

Patients and methods

PATIENTS

The study was carried out in the Special Care Baby Unit (SCBU) at the Rosie Maternity Hospital in Cambridge between December 1989 and October 1990. From a cohort of 74 consecutive admissions of babies with birth weight <1500 g, 30 remained longer than four weeks and were the subjects of this study. Infants were excluded only if they had a lethal congenital malformation, were admitted to the SCBU after 24 hours of age, or were less than the third centile for weight for gestational age. Informed consent was obtained from one or both parents. The study was approved by the district ethics committee.

METHODS

Recordings of CBFV were made using Duplex Doppler ultrasound (ATL Mk600) on day one and at weekly intervals thereafter until discharge. These were performed by a single operator. Doppler signals were processed using a microcomputer based system developed by Schlindwein and Evans.[12] This used a fast Fourier transform to calculate the peak velocity every 6·25 ms and passed the result to a second microcomputer (Apple Macintosh II running Labview) which was used to store the data. Each recording lasted one minute. Subsequently the velocity recording was visually inspected, and classified as showing variability at a frequency of between 1 and 5/minute, showing no such variability, or as unclassifiable. Variability at frequencies above 5/minute, probably due to the influence of respiration, was not considered in this study.

Amplitude of variability was then calculated by using the maximum systolic velocity present in the whole recording, subtracting the minimum systolic velocity, and dividing by the maximum systolic velocity. This was then expressed as a percentage.

We validated the visual classification of slow variability by comparing visual inspection with calculated values of maximum variability. A value of less than 10% maximum variability was used as a cut off for comparison with visual classification of no slow variability, as previous work has shown that short term variability is usually less than 10%.[13]

Each week study babies also had standard

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views of cerebral ultrasound recorded by skilled independent operators who assessed them for periventricular haemorrhage and for ischaemic lesions (periventricular leucomalacia).

Results

Altogether 133 recordings were obtained from 30 babies of mean birth weight 1113 g (range 573–1486) and mean gestational age 27 weeks (range 24–31). Postnatal age extended from birth to a maximum of 14 weeks. Babies ranged from those never ventilated to those ventilated for more than 28 days (table 1).

Six infants suffered a periventricular haemorrange of a grade greater than 2 (three grade 4, and three grade 3 according to the classification of Levene *et al*).[14] Four infants had ischaemic lesions, one with huge multifocal cysts, two with single anterior cysts, and one with multiple anterior cysts. One required shunting for posthaemorrhagic hydrocephalus. Slow variability was usually obvious, with only four recordings out of the 133 being unclassifiable. There was good agreement between visual classification and calculated amplitude of less than 10% (table 2).

Slow variability was sometimes present for only part of the minute recorded. When more than one cycle was observed, the cycle length was not always the same, meaning that the variability was not occurring at a constant frequency. The occurrence of slow variability decreased with increasing postconceptional age. All babies showed slow variability up to 26 weeks' postconceptional age, whereas this was observed in only 70% at 32 weeks and at 37 weeks this had fallen to 25% (fig 1). The 95% confidence intervals for this trend showed a significant reduction with increasing postconceptional age, as seen in fig 2A; babies were divided into four groups of increasing postconceptional age. Each group contained approximately equal numbers of babies.

A similar trend was seen with respect to postnatal age; the proportion showing epochs of no slow variability increased with increasing postnatal age. When 95% confidence intervals were calculated there was a significant difference between groups 1 and 3 and between groups 2 and 4 (fig 2B). In this instance groups consisted of babies of increasing postnatal age divided into periods of four weeks.

There was also a significant trend for damping of the amplitude of slow variability with increasing postconceptional age and with increasing postnatal age. Regression analyses of decreasing amplitude of variability with increasing age showed a significant correlation coefficient for seven of the eight babies with more

Table 1 Characteristics of study infants (n=30)

	Mean	*Range*	*No of infants*
Birth weight (g)	1113	573–1486	
Gestational age (weeks)	27·7	24–31	
No of days ventilated	9·3	0·5–44	
No of days in oxygen	41·1	1–200	
Periventricular haemorrhage:			
Grade 3			4
Grade 4			2
Periventricular leucomalacia			3 (1 severe)

Table 2 Comparison of visual inspection compared with measured amplitude of slow variation

	Validity of visual classification	
	Slow variability present	Slow variability absent
Maximum change in systemic velocity <10%	3 (false positive)	54 (true positive)
Maximum change in systemic velocity >10%	157 (true negative)	11 (false negative)
	Positive predictive value	94·7%
	Negative predictive value	93·5%
	Efficiency	93·8%
	False positive	1·9%
	False negative	19·3%

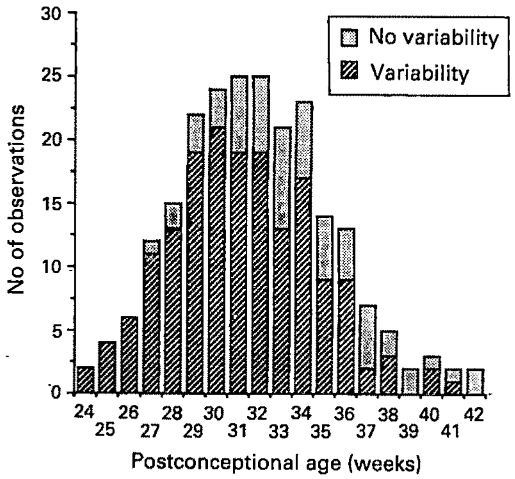

Figure 1 Presence of slow variability in CBFV related to postconceptional age.

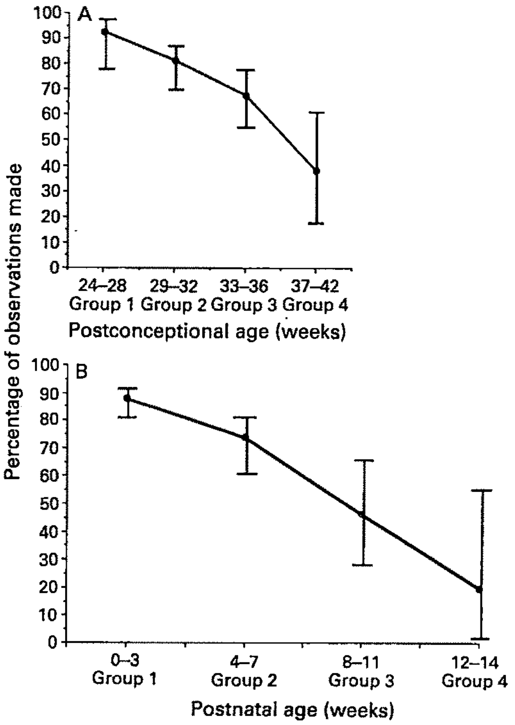

Figure 2 Presence of slow variability in CBFV related to (A) postconceptional age and (B) postnatal age showing the percentage incidence and 95% confidence intervals.

than nine recordings. Figures 3 and 4 show the epochs of CBFV recorded from one baby over 11 weeks, together with an example of such a regression analysis.

The pattern of evolution did not seem to relate to brain injury in the small group who sustained it except that, of the three who developed periventricular leucomalacia, one was the only baby who never demonstrated slow variability; the others showed slow variability up to the time of discharge. In the six with periventricular haemorrhage no particular pattern could be seen.

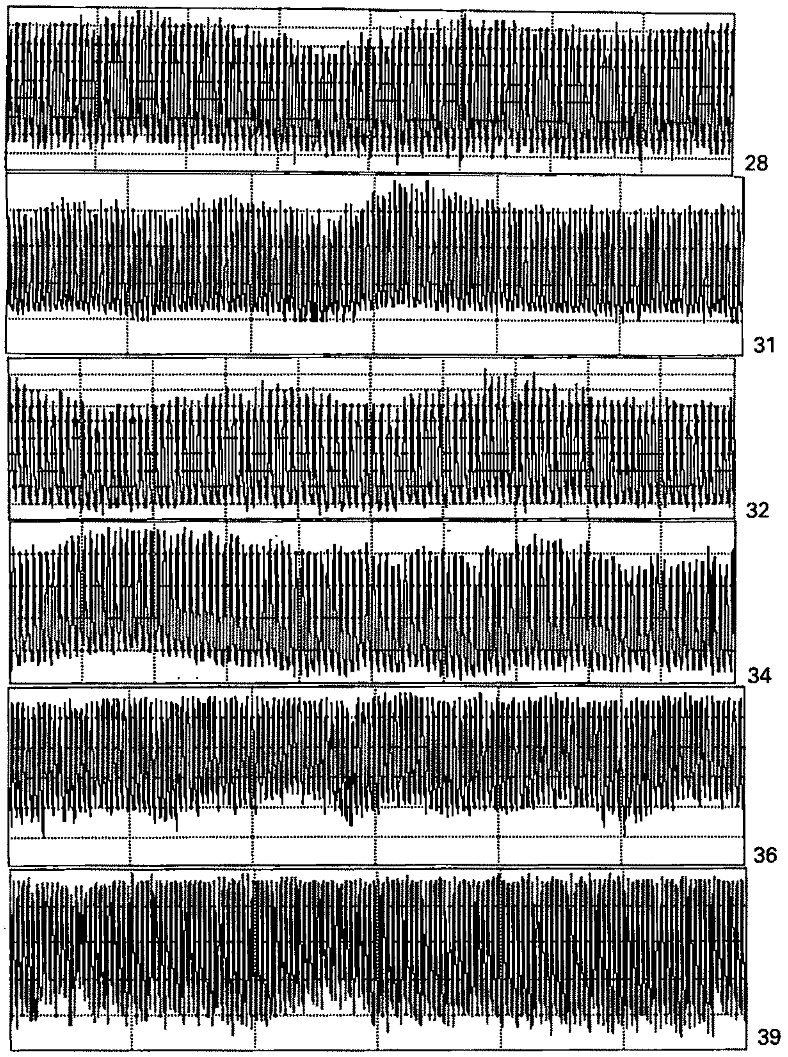

Figure 3 Evolution of slow variability in baby F from 28–39 weeks' postconceptional age.

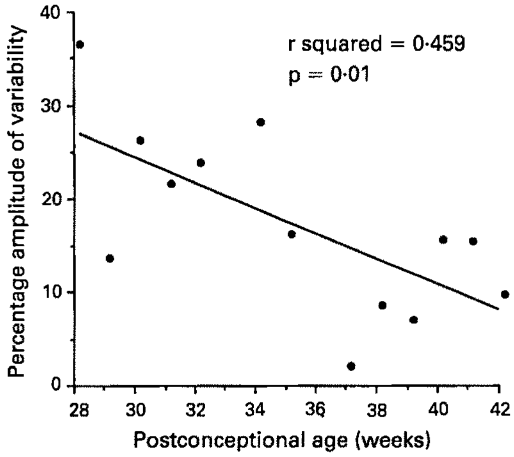

Figure 4 Regression analysis in baby F.

The disappearance of slow variability in CBFV could not have been due to truncation of the peak systolic velocity; the automatic scaling within the software always allows the maximum velocity to be displayed.

Careful inspection reveals the appearance of slow variability in the diastolic velocity of cerebral blood flow. This was observed in 19 infants, generally after 31 weeks' postconceptional age.

Discussion

This longitudinal study confirms the presence of slow variability in the CBFV of babies in the frequency range 1·5 to 5 cycles/minute as observed by Anthony *et al*[5]; it has also shown postnatal evolution of the activity.

Slow variability occurred in the majority of very low birthweight infants in the first weeks of life, being recorded at least once in 29 of the 30 babies. It appeared to be independent of the presence of respiratory distress syndrome and of severity of illness as some of the infants required no respiratory assistance while others required early inotropic support and ventilatory assistance for up to 44 days. As this study included only babies still in the nursery at 4 weeks of age it excluded early neonatal deaths. Also, although the study infants were entered from a consecutive cohort of babies of birth weight <1500 g, those still in the nursery by 2–3 months all had chronic lung disease so were a very selected group.

Perlman *et al* postulated that paralysis of sick preterm infants who had respiratory distress syndrome decreased beat to beat variability of CBFV and reduced the incidence of brain injury.[15] In this study administration of pancuronium, fentanyl, or morphine in seven babies did not affect the presence of slow variability. The pattern of slow variability did not differ significantly between those without intracranial pathology and those with either periventricular haemorrhage or periventricular leucomalacia. The single baby who showed no slow variability had the most severe intracranial pathology of all babies studied. This would support the fact that slow variability is a normal phenomenon in newborn babies, absent only in cases of extreme pathology. Indeed absence of any variability in heart rate is an adverse prognostic indicator for respiratory distress syndrome.[16] In severe respiratory distress syndrome, increased baseline heart rate and decreased variability may result from an increased concentration of circulating catecholamines which may represent abnormally high sympathetic activity.[17]

Since the original description of slow variability in blood pressure at a frequency independent of the respiratory frequency by Mayer,[3] two other areas of cyclical activity have been recognised in both heart rate and blood pressure: a peak around 0·05 Hz is thought to be related to fluctuations in peripheral vascular tone associated with thermoregulation and that around 0·12 Hz to the frequency response of the baroreceptor reflex.[7 8] Work in adults and in animals has shown that variability is influenced by thermoregulation and by pharmacological manipulation of the parasympathetic and sympathetic nervous systems. The renin-angiotensin system has also been shown to play a significant part in short term cardiovascular regulation, and blocking this system increases the amplitude of very slow cycles (0·04 Hz) in dogs.[18]

High variability in the region of vasomotor influence (0–0·1 Hz) relative to that in the region of respiratory frequency (0·25–1·0 Hz) is suggested to be a risk factor for sudden infant death syndrome and may represent slow maturation of the autonomic nervous system, with relative over-representation of the parasympathetic element.[19] In the study group of premature babies the reduction in amplitude of slow variability may represent a maturation of the balance between the two components of the autonomic nervous system. The cycle length of slow variability was variable, suggesting that several low frequency components were represented but the recording time was limited to 1 minute by the computer software. Much longer recordings would be required to resolve the frequency of several very slow variabilities with any degree of accuracy.

The significance of slow cycling in the diastolic velocity which appeared later in gestation in just over half of the babies has yet to be explained. We have no evidence that slow variability is harmful; further work may clarify the significance of this exaggerated normal response.

We would like to thank the nursing staff of the special care baby unit, Rosie Maternity Hospital, Cambridge, and Francis Griffiths for help with software.

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Intravenous aminophylline and cerebral blood flow in preterm infants

Maura McDonnell, N K Ives, P L Hope

Abstract

The effect of aminophylline on cerebral blood flow (CBF) was studied in 10 preterm infants who were receiving 6·2 mg/kg intravenously over 20 minutes followed by a maintenance infusion. CBF was measured intermittently using near infrared spectroscopy. Heart rate, blood pressure, oxygen saturation, and transcutaneously measured carbon dioxide tension (TcPCO_2) were recorded continuously. Aminophylline administration was associated with a fall in CBF from a median of 15·9 ml/100 g/min to 11·2 ml/100 g/min. Median fall in CBF was 4·1 ml/100 g/min (95% confidence interval 1·7 to 6·5). Heart rate rose and TcPCO_2 fell in all infants, median fall being 0·66 kPa. The reduction in CBF was greater than would be expected on the basis of the modest fall in TcPCO_2.

Aminophylline and other methylxanthines are frequently used in the neonatal period and have been reported to cause reduction in cerebral blood flow.[1] We have used near infrared spectroscopy (NIRS) to study cerebral haemodynamics and oxygenation before and after intravenous loading of preterm infants with aminophylline, according to the usual regimen for treatment of apnoea of prematurity on our unit.

NIRS is a non-invasive optical technique which provides continuous cotside measurement of the amounts of oxyhaemoglobin, reduced haemoglobin, and oxidised cytochrome aa3 in the light path between two optodes applied to either side of the infant's head.[2] Each of these three chromophores has a characteristic absorption spectrum for near infrared light. Light at six discrete wavelengths is transmitted from laser diodes to the head along fibreoptic cables. A sensitive photomultiplier detects the small amounts of light transmitted across the head, and the attenuation at different wavelengths can be used to calculate chromophore concentrations.

A transient increase in the infant's inspired oxygen concentration will cause a bolus of oxyhaemoglobin to enter the brain at a rate which is determined by cerebral blood flow (CBF) and can be measured by NIRS. CBF can be quantified in this way, using the method described by Edwards *et al.*[3]

Patients and methods

Ten preterm infants (gestation 23–31 weeks, median 26) were studied at 4–28 (median 9) days of age. Median birth weight was 830 g, range 519–2056 g. Seven of the infants were receiving mechanical ventilation, one was in headbox oxygen, and two were being treated with continuous positive airways pressure.

Aminophylline was prescribed for the treatment of apnoea of prematurity or to assist weaning from ventilatory assistance. A loading dose of 6·2 mg/kg body weight was given intravenously over 20 minutes and was followed by a maintenance infusion of 4·4 mg/kg/day. This regimen was recommended by Jones and Baillie on the basis of pharmacokinetic studies, and was calculated to give a serum concentration of 28–66 μmol/l one hour after loading.[4]

Oxygen saturation was measured by a pulse oximeter on the right hand working in beat to beat mode, and mean arterial blood pressure was measured through an umbilical or peripheral areterial cannula using a Hewlett-Packard pressure transducer. Heart rate, transcutaneous carbon dioxide tension (TcPCO_2), oxygen saturation, and mean arterial blood pressure were monitored continuously throughout the 2–4 (median 3) hour period of each study. Physiological measurements were stored on disc at 2–20 second intervals using the data storage system of the NIR spectrometer.

The near infrared measurements were made using the NIR-1000 (Hamamatsu Photonics KK) spectrometer. Optodes were applied to each temporal region, kept in place by an elasticated bandage, and covered by a light occluding hat which prevented contamination of the near infrared signal by external light. CBF was measured using a change in oxyhaemoglobin as a tracer. By the Fick principle, CBF can be calculated as the ratio of oxyhaemoglobin accumulated in the brain to the quantity introduced into the brain during a time period less than cerebral transit time (which is approximately 10 seconds). After a period when the oxyhaemoglobin signal and oxygen saturation were stable (with a saturation of 88–89%), the inspired oxygen concentration was suddenly increased in order to induce a transient increase in saturation of 5–8%. Cerebral oxyhaemoglobin and oxygen saturation were recorded at two second intervals during this manoeuvre for subsequent calculation of CBF.

CBF measurements were made on one to four (median three) occasions during the 135 minutes before drug infusion, and on one to five (median three) occasions in the 110 minutes after drug infusion. All infants were clinically stable during the period of the study. CBF values were not available 'on line' during the recording period. The near infrared and physiological data

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stored on disc in the spectrometer were transferred to a microcomputer spreadsheet for quantitative analysis at a later time. The data recorded during each brief period of induced rise in oxygen saturation were inspected, and all episodes in which data fitted a prospectively determined set of criteria were analysed and a CBF measurement determined. Measurements of physiological variables were taken during the periods of CBF measurement and later used in statistical analysis. Mean values of readings from each infant in the period before the drug were compared with mean values from the period after the drug was given using Wilcoxon signed ranks test for paired non-parametric data.

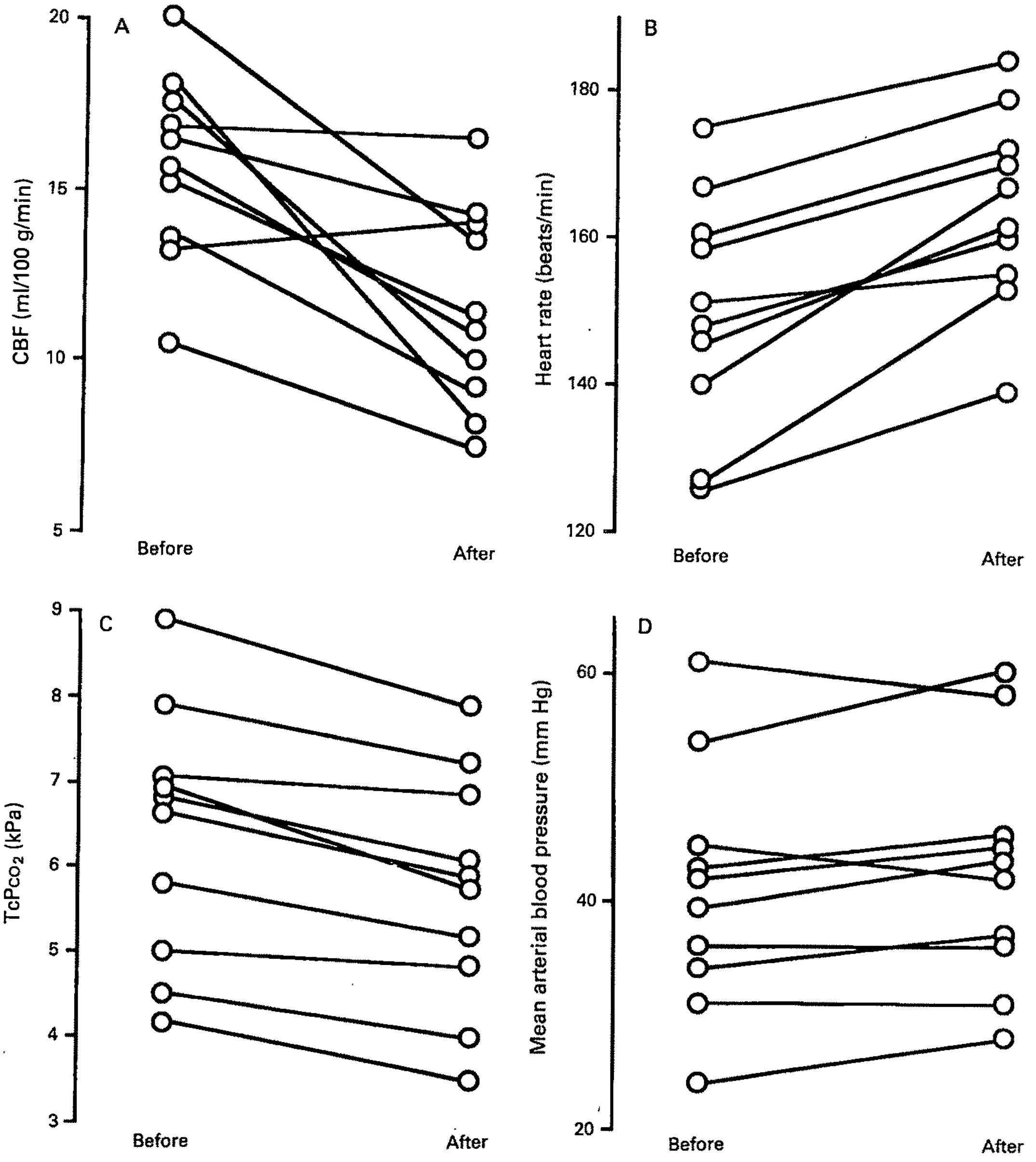
Results

Median CBF in the predrug period was 15·9 ml/100 g/min (95% confidence interval (CI) 13·5 to 17·7) and median CBF in the postdrug period was 11·2 ml/100 g/min. Eight infants showed a fall in CBF, one infant no change and one showed a 0·9 ml/100 g/min (6·9%) rise. The median fall in CBF was 4·1 ml/100 g/min (95% CI 1·7 to 6·5), or 28·9% (95% CI 12·3 to 37·7). Figure 1A shows the individual data points. The fall in CBF was significant on paired testing at $p<0·01$.

Figure 1B shows that heart rate rose in all infants ($p<0·01$), by a median of 12 beats/min (95% CI 9 to 19·2).

Figure 1C shows that a fall in $TcPco_2$ was demonstrated in all infants ($p<0·01$). Median fall was 0·66 kPa (95% CI 0·40 to 0·84). There was no consistent change in mean arterial blood pressure after aminophylline infusion (fig 1D).

If the changes in CBF (dCBF) after aminophylline were completely due to the changes in carbon dioxide tension ($dPco_2$), then a quantitative relationship between dCBF and $dPco_2$ would be expected. However, there was no significant correlation between dCBF and $dPco_2$, either expressed in absolute terms (correlation coefficient $r=0·57$, $n=10$, NS) or as a fraction of resting values ($r=0·49$, $n=10$, NS).



Paired values of (A) cerebral blood flow, (B) heart rate, (C) $TcPco_2$, and (D) mean arterial blood pressure before and after aminophylline infusion. (A), (B), and (C) show significant changes: $p<0·01$, using Wilcoxon signed ranks test; (D) shows no significant change.

Discussion

Aminophylline and other methylxanthines are commonly used for the treatment of apnoea of prematurity, and to assist weaning of low birthweight infants from mechanical ventilation. Preterm infants treated with methylxanthines show increased alveolar ventilation,[5] decrease in the incidence of apnoeic episodes,[5] and higher cardiac output due to increases in both heart rate and stroke volume.[6] These diverse effects are attributed to adenosine receptor antagonism, as very little phosphodiesterase inhibition occurs at therapeutic serum concentrations.[7] As adenosine is known to be a cerebral vasodilator, aminophylline may be expected to cause vasoconstriction and reduction in CBF.[7]

Wechsler *et al* in 1950 were the first group to show reduction in CBF after aminophylline administration.[8] Using the Kety-Schmidt method they showed a 25% fall in CBF of adults receiving an intravenous loading dose. The effect of methylxanthines on cerebral blood flow velocity (CBFV) of preterm infants has been measured by Doppler ultrasound in four studies. Rosenkrantz and Oh showed a 17% reduction in CBFV two hours after a 5 mg/kg bolus of aminophylline[9] which they attributed to a concomitant fall in Pco$_2$. Ghai *et al* found no change in Pco$_2$ or CBFV in 13 preterm infants studied 50 hours after starting enteral therapy.[10] Two recent studies have shown no effect of systemic doses of caffeine on CBFV in preterm infants,[11 12] although one of these studies[11] showed a significant fall in Pco$_2$. However, Doppler studies are difficult to interpret because CBFV may not reliably reflect CBF in this clinical situation when heart rate, blood pressure, Pco$_2$, and cerebral vessel diameter may all be changing. Pryds *et al*, using intravenous xenon^{133} clearance to measure CBF, reported a 13·8% reduction in CBF but unaltered visual evoked responses, one hour after 10 mg/kg intravenous aminophylline.[1]

NIRS can be used to determine cerebral blood flow with minimal patient disturbance. Since the description of the technique[3] there have been two reports validating the results of the NIR technique against xenon clearance methods.[13 14] Both NIRS and xenon clearance give surprisingly low values for CBF in the newborn, but they are consistent with values reported by Volpe *et al* using positron emission tomography.[15]

Nine infants in this present study had two or more measurements of CBF before the dose of aminophylline and the mean coefficient of variation of CBF measurement during this clinically stable period was 19% (95% CI 12·8–25·9). This coefficient is high and presumably reflects, at least in part, methodological limitations, but does not alter the significance of the changes in CBF seen on paired testing after aminophylline.

There was a small but consistent fall in Pco$_2$, but we do not consider this to be the full explanation for the considerable fall in CBF. Reported values for carbon dioxide reactivity of the cerebral circulation of preterm infants vary considerably. Pryds *et al* recently showed, using intravenous xenon^{133}, a 28·9% change per kPa change in Pco$_2$.[16] Using this value the fall in Pco$_2$ we have reported in this study would be expected to result in a fall in CBF of 19%, whereas a median decrease of 29% was actually observed. In addition, if decreased Pco$_2$ was the sole mechanism for the fall in CBF, there should be some relationship between the extent to which Pco$_2$ and CBF fall in individual infants, which was not demonstrated. It appears, therefore, that an intravenous loading dose of aminophylline leads to a fall in CBF which cannot be entirely explained by a small decrease in Pco$_2$.

A decrease of CBF, and hence cerebral oxygen delivery, will generally be compensated for by increased oxygen extraction resulting in a lower cerebral venous oxygen tension. There may be no clinical sequelae to considerable falls in CBF such as shown here with aminophylline treatment, or previously reported with indomethacin.[17] However, if cerebral oxygen delivery is already compromised in a sick preterm infant with hypotension and impaired oxygenation, further reduction of CBF of the magnitude reported in this study could potentially have serious sequelae.

We are very grateful to Hamamatsu Photonics (KK) for the generous loan of the NIR 1000 spectrometer, to Andrew Wilkinson for allowing us to study his patients, to Mr P Sutton for technical help, and to the nursing staff and parents for their cooperation.

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Upper airway patency during apnoea of prematurity

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Abstract

Twenty four preterm infants (median birth weight 1120 g and gestation 29 weeks) were studied on 83 occasions by measuring upper airway airflow. Airway patency was detected by the transmission of cardiac impulse up the airway and airway closure by its absence. A total of 309 apnoeas of at least five seconds' duration were recorded. One hundred and eighty (58·0%) were central, 109 (35·5%) mixed, and 20 (6·5%) obstructive.

Airway closure was noted in 47% of apparently central apnoeas. Airway closure occurred as apnoea lengthened; the airway remained patent in 38% of apnoeas of 5–9 seconds, 17% of those 10–14 seconds, and 11% of those 15–19 seconds' duration. Airway closure occurred in every apnoea of ≥20 seconds. As a consequence, closed apnoeas were longer than open apnoeas (mean 9·7 *v* 6·6 seconds).

In 72% of mixed apnoeas, airway closure was recorded during the central element and this usually preceded obstructive breaths. In 20% of mixed apnoeas and 15·5% of the total group the airways closed, having previously been patent. This occurred after a mean of 3·5 seconds (range 1–17). Mixed apnoea produced a significantly greater drop in arterial oxygen saturation than central apnoea, but only because of the greater duration of mixed apnoea.

Airway closure occurs in both central and mixed apnoea and appears to be important in the pathophysiology of mixed apnoea. Central and mixed apnoea are part of a continuum of airway closure and not separate entities.

Upper airways obstruction is an important factor which predisposes to the development of apnoea in preterm infants.[1] Pure obstructive apnoea is rare, however, occurring in 10–12% of apnoeas in published series.[1–3] Mixed apnoea, with both central and obstructive elements, is more common and its prevalence increases, relative to pure central apnoea, as apnoea duration lengthens.[2 3] It is not known, however, whether these two types of apnoea have different aetiologies, with mixed apnoea being intrinisically longer, or whether they are part of a spectrum, with initially central apnoeas becoming mixed as the apnoea continues.

Our group has previously reported that airway closure may occur during apparently central apnoea.[4] If airflow is measured at the mouth and nose during tidal breathing an artefact, produced by the transmission of the cardiac impulse up the patent airway, is also recorded. This cardiac artefact is usually present during central apnoea in preterm infants but disappears when airway closure occurs.

It has been demonstrated previously that the presence of the cardiac artefact is a reliable indicator of upper airway patency. All apnoeic episodes with a cardiac artefact present on the flow trace began at end expiration and if the artefact persisted until the end of the episode, the first respiratory effort always produced a tidal volume. In the absence of the artefact, apnoea could begin at other points in the respiratory cycle and in over half of these episodes the first respiratory effort did not result in a resumption of flow.[4]

We postulated that airway closure during central apnoea could result in mixed apnoea, and be detected by the absence of cardiac artefact. We have therefore serially studied a group of preterm infants to analyse this phenomenon in more detail and to determine its importance in the aetiology of mixed apnoea.

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Patients and methods

METHODS

Infants were studied in the right lateral position in their own cot or incubator, usually within an hour of a feed. No sedation was used. A flow of air of 3 l/minute from a cylinder was connected to one port of a Bennett face mask in order to eliminate dead space. The other port of the mask was connected by tubing to a Fleisch O pneumotachograph. Efferent flow, modified by the infant's inspiratory and expiratory effort, was recorded by the pressure gradient along the pneumotachograph, which was measured by a Validyne MP45 differential pressure transducer (range ±0·9 cm H_2O) and a transducer amplifier (P K Morgan No 076). The performance of the transducer was excellent and enabled accurate recording of the cardiac artefact in infants as small as 720 g. The 63% response time of the pneumotachograph and transducer, measured by a sudden closure of the barrel of a syringe connected to the apparatus, was 5 ms, giving a 3 dB/octave loss at 32 Hz. The total resistance of the mask system was 5·8 cm H_2O/l/second, measured at a flow of 3 l/minute.

Once the infant was asleep, the mask was placed over the mouth and nose, the seal being helped by the application of petroleum jelly to the rim of the mask. The flow signal was recorded on to tape (Racal, store 4) throughout the study, together with an electrocardiogram from a Life-Trace 12 monitor, arterial oxygen saturation (Sao_2) from an Ohmeda Biox 3700 monitor, and abdominal respiratory inductive plethysmography from a locally constructed model (Respivest). Additionally, the flow signal was recorded on to a chart recorder (Devices) together with the signal from a thoracic impedance monitor (Simonson and Weal respiratory 8061). Two channels representing respiratory effort were used to improve detection,[5] and the system has been described in more detail elsewhere.[6] Flow was recorded for between 20 and 30 minutes, as tolerated by the infant. Apnoeic episodes were later played on to a Gould chart recorder and analysed manually.

For the purposes of the study, apnoea was defined as cessation of airflow for 5 seconds or longer, and was regarded as central if there was no respiratory effort on the impedance and inductance traces. Apnoea was regarded as mixed if there was at least one obstructed breath and a central element of at least 3 seconds. If respiratory efforts continued, and/or the pause between efforts was less than 3 seconds, then obstructive apnoea was diagnosed. For each apnoea the presence or absence of cardiac artefact, the point in the respiratory cycle at which apnoea began and the drops in oxygen saturation were recorded.

Statistical analysis was performed using the Mann-Whitney U test, χ^2 test, simple regression, and stepwise multiple regression analysis. Approval for the study was given by the Nottingham ethics committee and informed parental consent obtained.

PATIENTS

The infants were not preselected for the presence of apnoea. The only entry criteria were a gestational age at birth of 32 weeks or less and being clinically stable in air at the time of study. Twenty four infants were studied, many longitudinally, on a total of 83 occasions. Median gestation was 29 weeks (range 25–32) and birth weight 1120 g (range 710–1700). Median day of study was 16 (range 2–55) at a median postconceptional age of 32 weeks (range 26–36). Thirteen boys and 11 girls were included and 41 studies were performed while receiving methylxanthine treatment for apnoea. Eight of the infants had received mechanical ventilation for up to 10 days before entering the study, but none had respiratory symptoms at the time. Three infants had ultrasound evidence of intraventricular haemorrhage but only one had any parenchymal changes and all were asymptomatic.

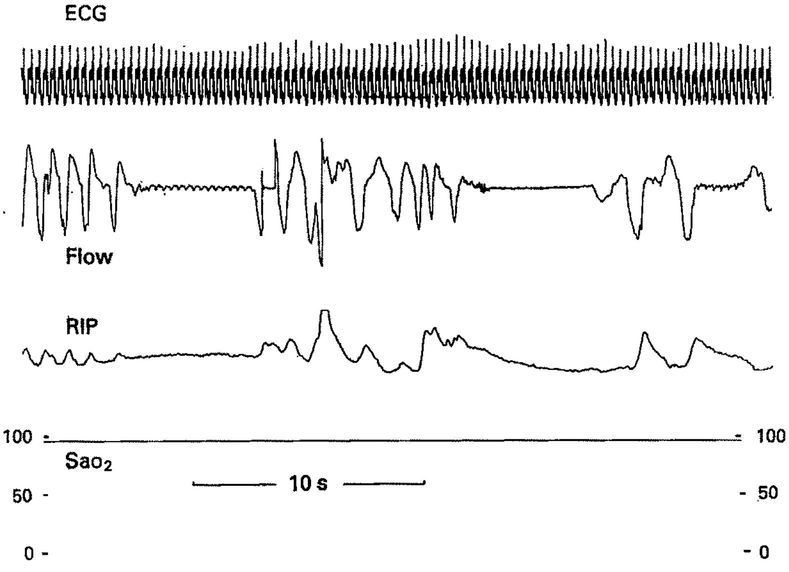

Figure 1 Two short central apnoeic episodes, the first with a patent and the second a closed upper airway. ECG, electrocardiogram; flow, upper airway flow; RIP, abdominal respiratory inductive plethysmography.

Results

AIRWAY PATENCY

Infants commonly became apnoeic during application of the mask and also during arousal, when they often strained against a closed glottis, as described by others.[7] Such episodes were excluded from analysis, leaving 309 apnoeic attacks for analysis. Episodes occurred in 60 of the 83 studies, with a median two apnoeas per study (range 0–19). A total of 180 apnoeas (58·0%) were central, 109 (35·5%) mixed, and 20 (6·5%) obstructive.

Two short central apnoeas are shown in fig 1. During the first episode the cardiac artefact is seen clearly throughout, indicating airway patency. However, during the second episode, which is also apparently a central apnoea, the cardiac artefact is not seen, indicating upper airway closure.

The relationship between apnoea classification and upper airway patency is shown in table 1. During only 53% of central apnoeas was upper airway patency maintained, and the airway was closed throughout during 30%. Nonetheless, this is not always the case. In fig 2 the cardiac artefact is not seen during the apnoea, and when breathing efforts resume after 12 seconds tidal exchange does not occur for a further 12 seconds and a mixed apnoea results.

The airway was closed throughout in 72% of mixed apnoeas, and this airway closure was evident even during the central element of the apnoea.

It is common, also, for airway patency to change throughout an apnoeic attack. This is usually a patent upper airway becoming closed as seen in fig 3, where the apnoea is classified as central, as tidal breathing resumes with the first respiratory effort. However, this pattern may also produce a mixed apnoea, as seen in fig 4. A patent airway closing was seen on 48 occasions (15·5% of the total), and approximately half of these were central and half mixed. This pattern was consistent with the commonest type of mixed apnoea, where the central element precedes obstructive breaths. This was seen in 69 of 109 mixed apnoeas, with obstruction prceding the central element on 40 occasions.

Table 1 Upper airway patency with respect to apnoea classification. Figures are numbers (%)

Upper airway patency	*Apnoea classification*		
	Central	*Mixed*	*Obstructive*
Open	96 (53)	5 (5)	1 (5)
Closed	54 (30)	78 (72)	18 (90)
Open→closed	25 (14)	22 (20)	1 (5)
Closed→open	5 (3)	4 (4)	0

The difference in the distribution is significant (χ^2, p=0·0001).

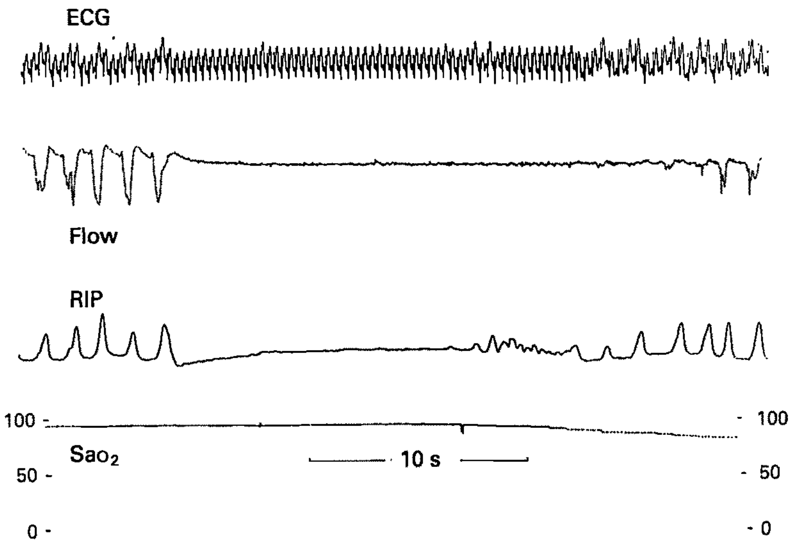

Figure 2 Prolonged mixed apnoea with airway closure even during the central element. ECG, electrocardiogram; flow, upper airway flow; RIP, abdominal respiratory inductive plethysmography.

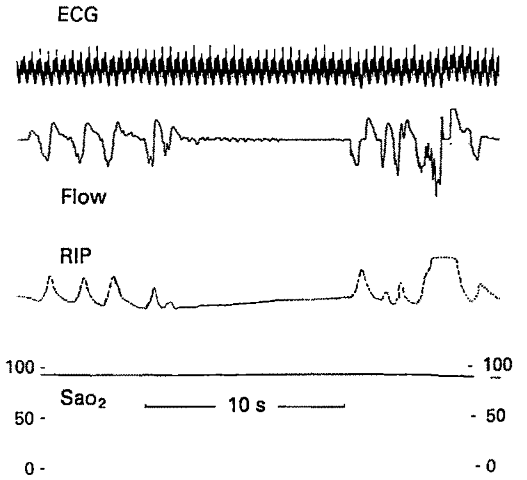

Figure 3 Central apnoea with a patent airway becoming closed. ECG, electrocardiogram; flow, upper airway flow; RIP, abdominal respiratory inductive plethysmography.

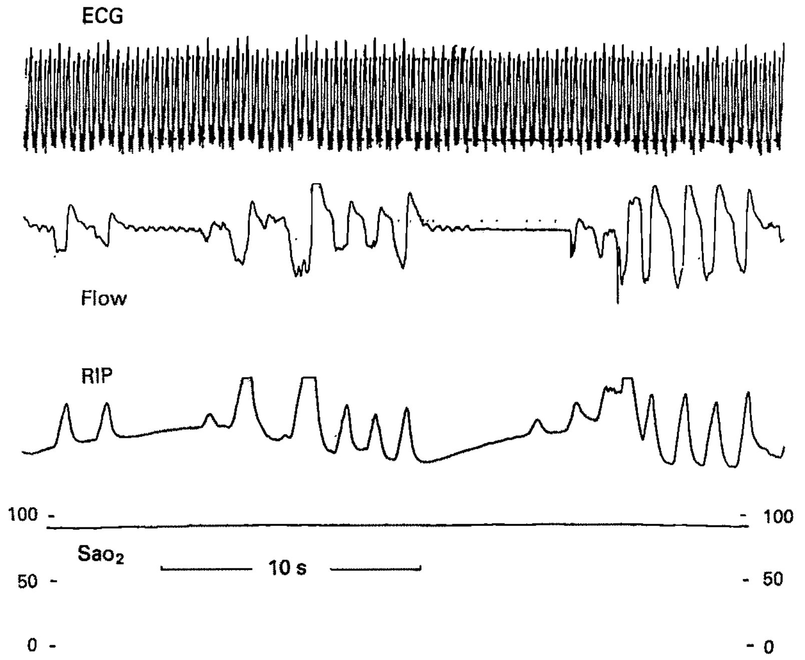

Figure 4 A patent airway closing and resulting in mixed apnoea. ECG, electrocardiogram; flow, upper airway flow; RIP, abdominal respiratory inductive plethysmography.

This was a significant difference ($p<0\cdot01$, χ^2 test).

A closed airway becoming patent without a resumption of breathing was also seen, as in fig 5, but was rare, occurring in only 2% of total apnoeas. Pure obstructive apnoea, usually with a closed airway throughout as shown in fig 6, was also rare. One apnoea with an open airway was classified as obstructive. This apparent paradox is explained by the difficulty in distinguishing breathing effort from body movement, even with two signals representing respiratory effort.

Confusion between respiration and body movement also explains the five mixed apnoeas with a patent airway. In retrospect, these few episodes with an apparently contradictory pattern have a high amplitude and disorganised trace on both respiratory signals, and almost certainly represent body movement rather than breathing effort. The difficulty in distinguishing the two is already well recognised.[7] Apart from these, when respiratory effort resumed with an open upper airway, tidal exchange occurred immediately.

As reported previously, apnoea usually begins at end expiration,[4] as seen in 284 of 309 apnoeas in this study. This was always the case when the upper airway was initially patent. On 19 occasions apnoea started in mid-expiration and on six occasions in mid-inspiration, with both these patterns resulting from airway closure.

Apnoea tends to become less common with increasing age, but the degree of airway closure did not appear to alter with age. There was no significant change in the percentage of episodes in which closure occurred with respect to either postconceptional or postnatal age. However, no infants were studied beyond 36 weeks' postconceptional age and improvement may have occurred later.

APNOEA DURATION

Mean apnoea duration recorded was 8·3 seconds (range 5–51 seconds). Apnoea duration divided by apnoea classification and airway patency is shown in table 2. Mixed apnoea was slightly longer than both central ($p<0\cdot0001$) and obstructive ($p<0\cdot02$) apnoea. Central and obstructive apnoea durations were not significantly different.

These observations are explained by the changing degree of airway patency at different apnoea durations. Airway closure becomes more common as apnoea continues. Complete airway patency was seen in 38% of apnoeas of 5–9 seconds, 17% of those 10–14 seconds, and 11% of those 15–19 seconds' duration. Airway closure occurred in every apnoea of 20 seconds' duration or greater. Consequently, closed apnoeas were significantly longer than open apnoeas ($p<0\cdot0001$). Airway closure *per se* appears to have an effect on apnoea duration. Episodes of central apnoea with airway closure tended to be longer than those which remained patent. There was a small but significant difference (mean 7·3 *v* 6·4 seconds, $p<0\cdot02$).

In the 48 episodes in which a previously

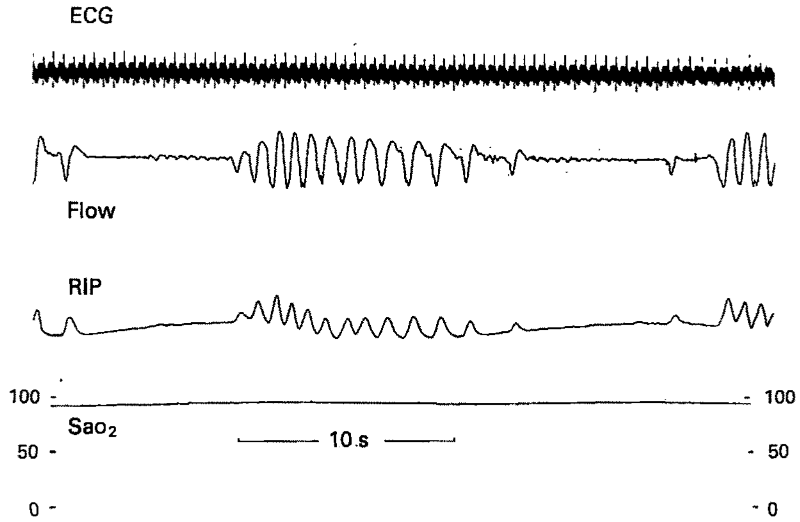

Figure 5 During the first episode here the closed airway becomes patent without apparent respiratory effort occurring. ECG, electrocardiogram; flow, upper airway flow; RIP, abdominal respiratory inductive plethysmography.

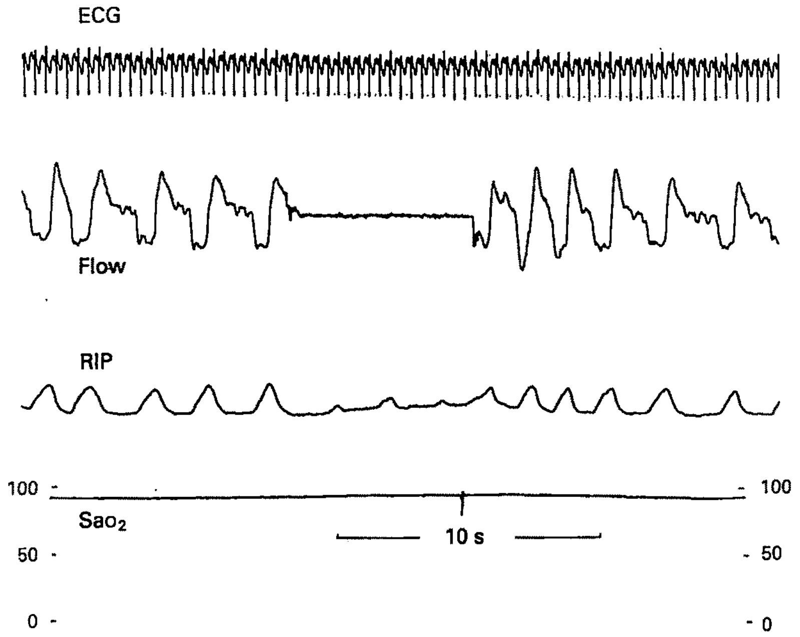

Figure 6 A short obstructive episode with closed airway throughout. ECG, electrocardiogram; flow, upper airway flow; RIP, abdominal respiratory inductive plethysmography.

Table 2 Apnoea duration (seconds) with respect to apnoea classification and airway patency

	Mean (SD)	*Median*	*Range*
Apnoea classification:			
Central (n=180)	6·8 (2·2)	6	5–19
Mixed (n=109)	11·0 (8·3)	8	5–51
Obstructive (n=20)	7·6 (3·4)	6·5	5–20
Airway patency:			
Open (n=102)	6·6 (2·0)	6	5–19
Closed (n=150)	9·7 (7·2)	7	5–51
Open→closed (n=48)	8·2 (4·6)	7	5–33
Closed→open (n=9)	6·0 (0·8)	6	5–7

patent airway closed the airway remained patent for a mean of 3·6 seconds (range 1–17); this was followed by a mean closed element of 4·6 seconds (range 1–16). Total apnoea duration during such episodes was not significantly different from closed apnoeas as a whole, but significantly longer than open apnoeas ($p<0·002$).

OXYGEN SATURATION

There was a close overall positive correlation between the Sao$_2$ drops during apnoea and apnoea duration (Sao$_2$ drop=(apnoea duration $\times$0·67)$-$1·0, r=0·75, $p<0·0001$). The Sao$_2$ drops during mixed apnoea were significantly greater than that during central apnoea (Median 5% *v* 2%, $p<0·0001$). However, this was purely a function of the longer duration of mixed apnoea because when the slopes of Sao$_2$ against duration for each class of apnoea were compared there was no significant difference.

To elucidate this further we performed a stepwise multiple regression analysis to look at the effects of apnoea duration, initial Sao$_2$ before the onset of apnoea, apnoea classification, and airway patency on the Sao$_2$ drop produced. As previously stated, apnoea duration was strongly related to Sao$_2$ but additionally there was a negative correlation between initial Sao$_2$ and Sao$_2$ drop ($p<0·0001$). Those with a low baseline Sao$_2$ desaturated further with apnoea than those who were well oxygenated. This negative correlation could have been predicted from the knowledge of the haemoglobin dissociation curve. However, neither the classification of apnoea nor the degree of airway patency had any significant effect on the drop in Sao$_2$.

Discussion

By serially studying a group of preterm infants we have been able to clarify the importance of patency of the upper airway and its closure, which may occur during apnoea. In roughly half of our apparently central apnoeas, airway closure was recorded. In 72% of mixed apnoeas the airway was also closed during the central element. That this same phenomenon is seen in both central apnoea and the central element of mixed apnoea is strong evidence that these two types of apnoea are part of the same pathophysiological process. Furthermore, closure of an airway that had previously been patent is also seen in both types. This pattern has only been reported once before,[4] but the use of a sensitive pressure transducer has enabled us to show that it is present in 15·5% of apnoeas. Airway closure occurs more commonly, though, at end expiration at the beginning of the apnoea. We have also noted that apnoea usually precedes obstructed breaths during mixed apnoea and that as apnoea continues the airway is increasingly less likely to be patent. In fact, airway closure always occurred in apnoeas of 20 seconds' duration or greater.

All these observations lead us to a unified hypothesis by which mixed apnoea may be explained. Central apnoea occurs at end expiration and in half of these episodes the airways remains patent. Spontaneous recovery then commonly occurs, although some infants go on to develop airway closure. Of those episodes with airway closure the first respiratory effort may overcome the obstruction, in which case the episode is still outwardly central in appearance. However, a proportion are not terminated by the first respiratory effort and mixed apnoea results.

Clearly, during the minority of mixed apnoeas in which obstructive breaths precede the central element, and also obstructive apnoea itself, a different mechanism is in operation. Obstruction, for whatever reason, occurs first and in a proportion of these precipitates apnoea, during which the airway is usually closed. That obstruction may precipitate a cessation of respiratory effort in infants is well documented.[8 9]

Our results and the above hypothesis fit well with previously published observations.[1–3] The one major difference is the smaller number of pure obstructive apnoeas which we have detected. Care needs to be taken in applying a facemask over an infant's mouth and nose, particularly to avoid neck flexion which may precipitate obstructive apnoea.[10] However, we were careful to study infants with their necks in a neutral position. Indeed, if the mask had affected our number of apnoeas, then we would have expected an increase in the relative proportion of obstructive apnoeas. Infants are not obligatory nose breathers,[11] and it is possible that some infants in our study used oral breathing in response to nasal obstruction. The studies of Butcher-Puech *et al*[2] and Muttitt *et al*[3] used nasal flow and may have classified episodes of oral breathing as obstructive apnoea. However, this was not noted to be important in the study of Dransfield *et al*,[1] nor in older infants with apnoea.[7] We have included short apnoeas of 5–9 seconds' duration in our study in order to look at airway closure. This is not likely to affect the proportion of obstructive apnoeas as these are usually short and, in fact, if only apnoeas of $\geqslant 10$ seconds are considered the relative proportion of obstructive apnoeas drops to 5%. The most likely difference between our study and others is that we used two signals of respiratory effort, which helped us distinguish this from body movement. The previous studies each used only one signal and may have classified mixed or central apnoea with body movement as obstructive apnoea.[1–3] This has been discussed in detail by Van Someren and Stothers.[7] The prevalence of obstruction may have been even lower if we had used oesophageal pressure measurements as in our previous study[4]: although the total number of apnoeas was smaller, there were no episodes of pure obstructive apnoea.

Mixed apnoea is clearly more common than obstructive apnoea. It is also more significant, as it results in a larger fall in Sao_2. This greater Sao_2 drop, however, is purely a consequence of the greater duration of mixed apnoea, rather than any direct effect of obstruction on the rate of fall of Sao_2. This is supported by the study of Muttitt *et al*,[3] but is in contrast to work in older infants,[12] although the number of obstructive episodes in this latter study was very small.

This study has elucidated the role of airway closure in apnoea in general, and mixed apnoea in particular. Two important questions remain unanswered, though: What is the mechanism by which airways closure occurs? and Where is the site of obstruction?

Closure of the airway could simply be a passive phenomenon, with tone being lost in the upper airway when flow ceases during central apnoea. The greater predisposition of preterm infants to airway closure with apnoea would then be explained by the narrower lumen making complete closure more likely.[13] However, studies on animals under anaesthesia compared with studies postmortem have shown that there is active maintenance of upper airway patency, mainly by genioglossus and geniohyoid, which prevents upper airway closure.[14] Additionally, genioglossus activity is linked closely to that of other respiratory muscles,[15] and there is evidence that flow through the upper airway results in feedback from airway receptors to maintain genioglossus tone.[16] Therefore, it is possible that both the relaxation of other respiratory muscles and the cessation of upper airway flow may actively inhibit genioglossus activity, resulting in airway closure. Although passive forces may play a part in this, the fact that we have occasionally seen upper airway patency being restored in the absence of respiratory effort, would tend to support the concept that airway patency and closure are actively determined.

The site of airway obstruction has yet to be defined. From our initial study we postulated that laryngeal closure was likely,[4] but work using pressure sensitive pharyngeal catheters has suggested that upper pharyngeal closure is responsible.[17] One criticism of the use of such catheters is that placement has to be precise, making interpretation of results difficult. We are now performing direct upper airways endoscopy in infants with apnoea in order to visualise the site of airway obstruction. Preliminary studies have suggested that closure of the arytenoid masses and aryepiglottic folds across the vocal cords may be important.[18]

We are grateful to the Medical Research Council of Great Britain for financial assistance.

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Caffeine or theophylline for neonatal apnoea?

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Abstract

Caffeine, in the dose usually recommended (12·5 mg/kg loading dose and 3 mg/kg daily maintenance), and a higher dose regimen (25 mg/kg loading and 6 mg/kg daily maintenance), was compared with theophylline (7·5 mg/kg loading and 3 mg/kg thrice daily maintenance). The study was a randomised controlled trial in the treatment of a group of 44 infants of less than 31 weeks' gestation (mean gestational age 28·3 weeks) who were suffering from frequent apnoeic attacks. All three regimens produced a significant reduction in apnoeic attacks within 24 hours, but only the higher dose caffeine and theophylline groups showed a significant improvement in apnoea within eight hours.

The use of caffeine for the treatment of neonatal apnoea is recommended, because a once daily dose is more easily administered, and because it was found that plasma concentrations were more predictable than those of theophylline. If used in very preterm infants, however, its is suggested that a higher dose regimen than that previously recommended be used to achieve a faster response.

Neonatal apnoea is a common problem: it occurs in 25% of infants under 2500 g and 80% of infants under 1000 g.[1 2] With smaller babies now forming a large percentage of the population of neonatal intensive care units, the management of neonatal apnoea is an important part of the clinical workload.

The methylxanthines—theophylline (and aminophylline) and caffeine—are widely used for the treatment of this condition.[3] Theophylline has been the drug most commonly used to treat neonatal apnoea in the UK.[4 5] Caffeine, however, has many potential advantages: it has a higher therapeutic ratio, it is absorbed more reliably when administered enterally and has a longer half life, thus enabling the drug to be administered only once daily.[6] Caffeine has also been shown to be effective in apnoeic infants who are unresponsive to theophylline.[7]

Comparisons of the two drugs have been reported before,[8–10] but these studies have either included a high proportion of more mature infants (of 31 or 32 weeks' gestation), excluded oxygen dependent infants or included infants with as few as three apnoeas per day. They therefore failed to reflect the day to day problems in most neonatal intensive care units in their management of very preterm infants with apnoeic attacks.

In a pilot study we formed an impression that a higher dose of caffeine than that previously recommended was required to treat effectively infants of lower gestational age. This study was therefore designed to compare the efficacy of theophylline with that of caffeine administered in two different dose regimens to a group of very preterm infants with frequent and clinically significant apnoeic attacks.

Patients and methods

PATIENT SELECTION

Infants were included in our study if they were less than 31 weeks' gestation at birth and if they had either 10 (or more) apnoeic attacks in eight hours or four apnoeas in one hour. Apnoea was defined as a drop in heart rate of more than 40 beats/minute (bpm) below the resting heart rate in an infant who was not breathing, and who required stimulation to correct the problem.

Infants prospectively entering the trial were randomly allocated (by random numbers in sealed envelopes) to one of three treatment groups. *Group A* ('standard dose caffeine')—a loading dose of 25 mg/kg caffeine citrate (12·5 mg/kg caffeine) and a maintenance dose of 6 mg/kg caffeine citrate (3 mg/kg caffeine) once daily were given to produce a desired plasma concentration of 15 mg/l caffeine (range 13–20 mg/l). *Group B* ('higher dose caffeine')—a loading dose of 50 mg/kg caffeine citrate (25 mg/kg caffeine) and maintenance dose of 12 mg/kg (6 mg/kg caffeine) once daily were given to produce a desired plasma concentration of 30 mg/l (range 26–40 mg/l). *Group C* ('theophylline')—a loading dose of 7·5 mg/kg theophylline and a maintenance dose of 3 mg/kg theophylline three times daily were given to produce a desired plasma concentration of 15 mg/l (range 13–20 mg/l).

In all three treatment groups the maintenance dose of the drug was adjusted if the plasma concentrations were out of the desired range, but in none of these patients were such adjustments made within 48 hours of starting treatment. As theophylline is metabolised into caffeine in the premature infant,[11] the cumulated caffeine plus theophylline concentrations in this group were kept below 25 mg/l.

DRUGS

The drugs were usually given orally or via a nasogastric tube. The preparations used for oral administration were caffeine citrate in chloroform water (20 mg caffeine citrate/ml) and theophylline hydrate in 90% alcohol diluted with water (3 mg theophylline/ml). Although

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these are the preparations that we are still using, recent work has shown that the preservatives in these mixtures (that is, chloroform water and 90% alcohol) are not essential, and that caffeine and theophylline are pharmacologically stable and microbiologically safe for a period of one week having been made up in purified water and stored in a refrigerator (Tina Crook, Royal Berkshire Hospital, pharmacy department—personal communication).

When using the 'higher dose caffeine' regimen the loading dose was administered in two separate doses of 25 mg/kg caffeine citrate given orally one hour apart, in order to avoid the possibility of the infant vomiting because of the volume load.

Caffeine citrate 0·99% (caffeine citrate 10 mg/ml)—both loading dose and maintenance doses infused daily over half an hour—and aminophylline injection (aminophylline 25 mg/ml)—administered as a continuous infusion—were available as alternatives to oral or nasogastric treatment in our trial. None of the infants in group B (higher dose caffeine) or group C (theophylline) received intravenous treatment. Only two infants in group A (standard dose caffeine) received intravenous caffeine, and neither their clinical response nor the plasma concentrations of caffeine different appreciably from the other infants in that group. We have treated large numbers of other infants with both caffeine citrate and aminophylline administered intravenously, and have observed no differences, clinically or with plasma concentrations, related to route of administration.

MEASUREMENTS OF PLASMA CONCENTRATIONS OF THE DRUGS

Blood samples for measurement of drug concentrations were obtained at the same time as blood sampling for other routine tests: all were heparinised capillary samples taken from the heel. They were obtained daily for five days, starting the day after the loading dose, and twice during the course of the next week. Plasma theophylline and caffeine concentrations were determined by high performance liquid chromatography on 100 µl of plasma (minimum 50 µl plasma).

Table 1 Characteristics of infants entering the trial (n=44). Weight and age figures are mean (SD)

	No of infants	*Birth weight (g)*	*Gestational age (weeks)*	*Postnatal age (days)*	*M:F ratio*
Group A (standard dose caffeine)	16	1140 (210)	28·7 (1·2)	5·6 (2·6)	9:7
Group B (higher dose caffeine)	14	1200 (260)	28·2 (1·1)	6·0 (2·7)	7:7
Group C (theophylline)	14	1240 (320)	27·9 (1·4)	7·6 (4·9)	8:6

Table 2 Effect of treatment in reducing the number of apnoeas. Figures are mean (SE)

	Reduction in the number of apnoeas		
	No of apnoeas/ 24 hours (day 0)	*Reduction between day 0 and day 1*	*Reduction between day 0 and day 2*
Group A (standard dose caffeine)	22·81 (0·49)	−6·94 (0·69)*	−12·50 (0·67)***
Group B (higher dose caffeine)	22·79 (0·72)	−12·79 (0·63)***	−17·14 (0·57)
Group C (theophylline)	24·07 (0·70)	−13·86 (0·86)**	−20·36 (0·74)

Significance: *0·05>p>0·02; **0·01>p>0·001; ***p<0·01.
Day 0 is the day before treatment started.

STATISTICS

Statistical analysis of results was performed using Fisher's exact test and Student's paired *t* test as appropriate.

This project was approved by the ethical committee of Central Birmingham Health Authority.

Results

Over a two year period 44 infants were entered into the study. Of the 44 infants, 32 (73%) had previously been ventilated and 43 (98%) were still oxygen dependent at the time of entry to the study. Twenty six infants (59%) were boys and 37 (84%) were white.

Although every attempt was made to exclude other causes of apnoea, eight infants were subsequently found to have other problems and it became clear that their apnoeic attacks were secondary to these other diagnoses: four infants had proven infection (pneumonia and septicaemia with positive blood cultures), two infants had significant neurological abnormality (bilateral periventricular leucomalacia with subsequent abnormal neurological development) and two had severe oesophageal reflux (as demonstrated by an intraoesophageal pH probe.[12]

Table 1 shows the characteristics of the infants in the trial. There were no significant differences between the groups in weight, gestational age, or postnatal age and the sex distribution of the infants within the groups showed an approximately equal male to female ratio.

RESPONSE TO TREATMENT

The number of apnoeas (over a 24 hour period) decreased dramatically over two days from the start of treatment in all three groups, but was most significant in the high dose caffeine and theophylline groups.

As can be seen in table 2, which includes the results from all infants entered, the number of apnoeas/day was reduced by a third within 24 hours by treatment with standard dose caffeine. It was, however, reduced by over 50% by the higher dose caffeine and theophylline treatments within the same time period. Although a further reduction was observed in the standard dose caffeine group by 48 hours, some infants in the other groups had, by then, had their apnoeas eliminated completely.

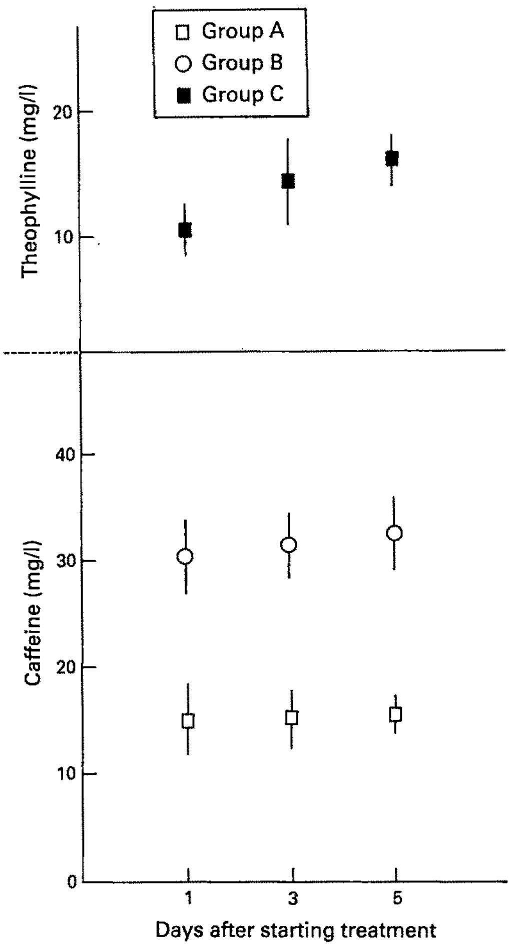
We defined successful treatment as a >50% reduction in the number of apnoeas (as measured over an eight hour period). Only one infant, other than those whose apnoea was retrospectively found to be secondary to another diagnosis, failed to respond within 48 hours of the start of treatment. The response to treatment is illustrated in table 3: those infants who subsequently had other pathology are excluded, rather than being described as 'failures'.

In group A only four of the 12 infants responded to treatment within eight hours.

Table 3 Response to treatment, where success is defined as >50% reduction in the number of apnoeas

	Success			*Failed*	*Excluded*
	<8 hours	*<24 hours*	*<48 hours*		
Group A (standard dose caffeine)	4	2	5	1	4
Group B (higher dose caffeine)	10	1	1	0	2
Group C (theophylline)	11	1	0	0	2

Comparing success at 8 hours: group B>group A p=0·036; group C>group A p=0·01.



Plasma drug concentrations, shown as mean (SD). Group A: standard dose caffeine; group B: higher dose caffeine, and group C: theophylline.

Another seven had a >50% reduction in apnoeas by the end of 48 hours. Only one infant failed to respond (no explanation for this failure could be found). Two infants in this group received their treatment parenterally: one responded with a reduction in apnoeas of >50% within eight hours, the other took 48 hours to respond in the same way. There were no differences observed between these two infants and the rest of the group (clinically or in their plasma concentrations).

In group B 10 of the 12 infants responded to treatment within eight hours. Another two had responded by the end of 48 hours. There were no failures in this group.

In group C 11 of the 12 infants responded to treatment within eight hours. Another had responded by 48 hours. There were no failures in this group either.

All eight infants who were retrospectively excluded failed to respond with a >50% reduction in apnoeas within 48 hours of starting treatment. Three of the infants who responded to treatment also had other problems: two with periventricular leucomalacia, both in group C, and one with oesophageal reflux in group B. The two with periventricular leucomalacia, however, had unilateral lesions (and a better neurological outcome than those with bilateral lesions who were excluded); and the infant with oesophageal reflux appeared to have less severe reflux, although it may have remained a cause of apnoea (he had a >50% reduction in apnoeas within eight hours, but then persisted with a small number of severe apnoeic attacks each day).

PLASMA DRUG CONCENTRATIONS

The figure shows the plasma drug concentrations in the three treatment groups on the first, third, and fifth day after starting treatment (approximately 24, 72, and 120 hours after starting treatment respectively). The mean (SD) plasma concentrations of caffeine in group A on days 1, 3, and 5 were 15·43 (5·11), 15·31 (3·93), and 15·81 (2·90) mg/l respectively. In group B the plasma concentrations of caffeine were: 30·42 (4·05), 32·92 (4·88), and 33·36 (5·27) mg/l. The plasma concentrations of theophylline in group C were: 10·87 (3·52), 14·96 (6·00), and 17·22 (3·19) mg/l.

Over the 10 days during which plasma drug concentrations were monitored, 69% of the measurements on infants in group A showed drug concentrations in the desired range (caffeine 13–20 mg/l), and 73% of the assays on infants in group B were in the desired range (caffeine 26–40 mg/l). In contrast, only 56% of the measurements on infants in group C showed plasma drug concentrations in the desired range (theophylline 13–20 mg/l).

SIDE EFFECTS

Plasma concentrations of theophylline >20 mg/l were associated with a persistent tachycardia (of >195 bpm), necessitating a dosage reduction, in two infants. Five of the 12 infants in group C required dosage adjustments, or individual dose omissions on at least two occasions, because of a tachycardia of >195 bpm. Only one of the infants in group A, and none of the infants in group B, needed dosage adjustments because of tachycardia. Apart from this one infant whose tachycardia may have been attributable to treatment, no side effects were apparent with caffeine, even when an error occurred in calculation of the caffeine dose (on the fourth day of treatment in one child), and a plasma concentration of 68 mg/l was measured.

The maximum effect on heart rate (the average of all 24 on-the-hour recordings by nursing staff expressed as bpm) was observed on the fourth day of treatment, with a mean rise in heart rate of 3 bpm and 5 bpm in groups A and B ($p<0·05$ on paired *t* test), and a mean rise in heart rate of 12 bpm in group C ($p<0·01$).

There was no appreciable difference between the sodium intake, urinary sodium, or fractional sodium excretion of the three groups over the 10 day period. Any natriuretic (diuretic) effect of the medication was probably masked by the high sodium loss which is commonly observed in the urine in infants of these gestations.

Although these drugs in higher doses are reputed to have side effects such as glucose intolerance and 'jitteriness', we observed no such problems. In fact, no serious side effect was attributed to medication in any treatment group.

Discussion

Our study confirmed the efficacy of the methylxanthine drugs, caffeine and theophylline, in the treatment of neonatal apnoea. However, unlike previous reports,[3 8–10] our study is based on infants of lower gestational age (less than 31 weeks); these infants were oxygen dependent. Furthermore, there is no previous information on the response rate in relation to caffeine dosage.

Our results clearly showed a significant rapid reduction in apnoeic attacks within eight hours in infants receiving higher doses of caffeine (plasma concentration approximately 30 mg/l) and theophylline. A rapid response to treatment is valuable and often desirable as intubation or reintubation for ventilation may be avoided.

Despite using a higher caffeine dose, the plasma drug concentrations in all infants were well within the reported therapeutic range.[3] Our highest caffeine concentration was 68 mg/l. None of our infants on the higher dose of caffeine suffered any adverse side effects. Anyway, side effects such as glucose intolerance, appreciable tachycardia (>200 bpm) and 'jitteriness' are thought to be rare with plasma caffeine concentrations below 80 mg/l.

In our experience plasma caffeine concentrations were more likely to fall within the predicted range than theophylline, when the drugs were given orally, suggesting better absorption of caffeine. In addition, the known longer half life of caffeine and its higher therapeutic ratio, enable fewer blood tests when using caffeine to treat neonatal apnoea.

In conclusion, our study has shown that caffeine (in the higher dose studied) and theophylline (in a standard dosage) are effective in reducing apnoeic attacks within eight hours, even in oxygen dependent infants of less than 31 weeks' gestational age. However, we recommend the use of caffeine because of the many advantages of this drug over theophylline.

Our current practice is to treat symptomatic babies with the higher dose caffeine schedule described here, and to measure plasma concentrations of caffeine only if there is inadequate clinical response.

The authors would like to express their thanks to all the nursing staff in the Regional Neonatal Intensive Care Unit for so carefully documenting the apnoeas—and for keeping so many small babies breathing. Without their skills this study would not have been possible. Our thanks are also due to Dr George Rylance at Birmingham Children's Hospital for his helpful advice.

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Randomised trial of continuous nasogastic, bolus nasogastric, and transpyloric feeding in infants of birth weight under 1400 g

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Abstract

Forty three infants under 1400 g were fed by a bolus nasogastric, continuous nasogastric, or transpyloric route. There were more complications with transpyloric feeding and no identifiable benefits in the growth rate, oral energy input, or chosen biochemical indices of nutrition. Bolus or continuous nasogastric feeds rather than transpyloric are better routine methods in infants of low birth weight.

Feeding tiny preterm infants is vitally important and yet may be very difficult. Transpyloric feeding has been used widely in the past. However, different comparisons with nasogastric feeding have produced conflicting results.[1–3] This study compares the growth of babies randomised to receive one of three methods of feeding: hourly bolus nasogastric feeding (bNG), continuous nasogastric feeding (cNG) and continuous transpyloric feeding (TP).

Patients and methods

A one year prospective study (January to December 1987) enrolled 43 infants of birth weight under 1400 g. The babies initially received total parenteral nutrition. On day 2 the feeding route was determined for each baby by opening a sealed envelope, and milk feeding started with 1 ml/hour of SMA low birthweight formula (Wyeth). Milk feeds were increased by increments of 0·5 to 1·0 ml/hour and supplemented with parenteral nutrition until such time as the infants were tolerating full energy and fluid requirements given as the low birthweight formula at 150 ml/kg a day.

The position of the nasogastric tubes was confirmed by aspiration and pH testing. Transpyloric tubes were sited in the second and third part of the duodenum and the position was confirmed radiologically. The infants were fed by the selected method until they reached a weight of 1600 g after which they all received bolus nasogastric feeding. No baby received energy supplements during the trial period. Infants who received expressed breast milk were excluded from the trial as were those with major congenital malformations, those who developed hydrocephalus, and those with intrauterine viral infections. Weekly anthropometric measurements of length (using the Pedobaby babymeter), weight, and occipitofrontal circumference were made. In addition triceps and quadriceps skinfold thicknesses were measured.

Weekly blood samples were obtained and analysed using standard biochemical methods for alkaline phosphatase (German Optimised method: EC3.1.3.1.), urea (urease method), albumin (bromocresol purple method),[4] prealbumin, and transferrin (both were assayed by immunodiffusion and immunoturbidimetric methods). Prealbumin,[5] transferrin,[6] and albumin[7] were chosen as useful indices of protein nutrition with their differing half lives of two days, eight days, and 20 days respectively.

Fifteen babies started in the TP group, but only 10 completed the study as three died before milk feeding was established, one was transferred to another hospital aged 2 weeks, and in one it proved impossible to site a feeding tube distal to the pylorus despite five attempts. Thirteen babies enrolled in the cNG group, one of whom was transferred to another hospital aged 2 weeks, while 12 completed the study. Fifteen babies enrolled in the bNG group, three of whom died before milk feeding was established, leaving 12 to complete the study. All deaths were within the first week, five being due to massive intraventricular haemorrhage in babies between 24 and 28 weeks of gestation. The other death was due to severe respiratory distress syndrome with unresponsive respiratory failure in an infant of 30 weeks' gestation.

Mean birth weight (g) and range of the survivors in each group was: TP 1177 g (840–1400), bNG 1203 g (740–1400), cNG 1137 g (860–1390). Mean gestation in weeks and range was: TP 28·9 (26–32), bNG 29·1 (25–34), cNG 28·5 (26–32). In each nasogastric group nine out of 12 were ventilated and in the transpyloric group seven out of 10 were ventilated.

Results

Each infant's daily energy input per kilogram, achieved in the form of milk, was calculated for the first four weeks or until exit from the study at 1600 g or whichever occurred first. There was no significant difference in milk input between any of the groups during this period (one way analysis of variance on log transformed data) (table 1). Comparison of the mean daily energy

Table 1 Daily oral energy input (mean (SD) values measured in kJ/kg/day)

	Feeding group		
	TP	*cNG*	*bNG*
Week 1	160 (109)	164 (97)	134 (101)
Week 2	365 (168)	349 (181)	386 (151)
Week 3	370 (189)	378 (189)	420 (185)
Week 4	399 (176)	378 (197)	403 (155)

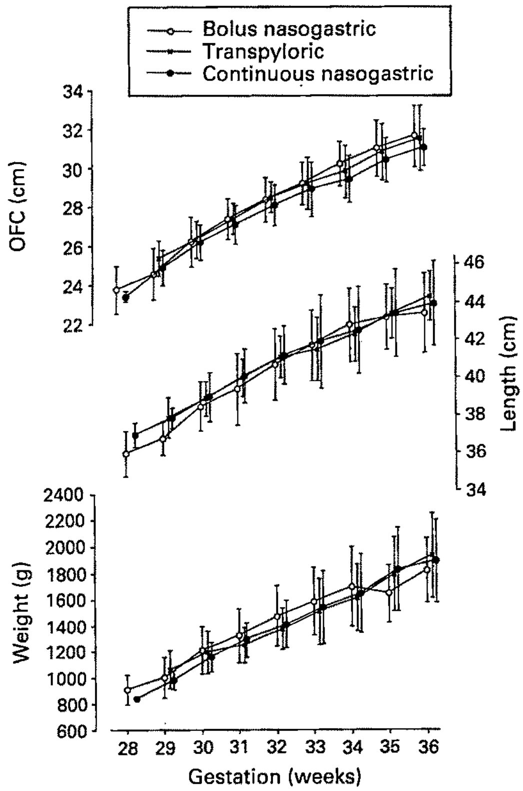
TP, transpyloric; cNG, continuous nasogastric; bNG, bolus nasogastric feeding.

input of the three groups once they were no longer receiving any supplementation with parenteral nutrition also shows no significant difference (one way analysis of variance): TP 496 kJ/kg/day, cNG 512 kJ/kg/day, bNG 487 kJ/kg/day with pooled SD 46·6.

There was no significant difference between the groups (one way analysis of variance) in the length of time required to achieve full enteral feeding (bNG mean 18·6 days, cNG mean 20·7 days, TP mean 15·8 days with pooled SD 17·8). However, there were two babies in each nasogastric group who took more than 50 days to tolerate full enteral feeding while the maximum time required in the TP group was 37 days.

Each infant's weight, length, and occipitofrontal circumference were plotted against gestational age; mean (SD) was calculated for each group weekly up to 36 weeks of gestation. On the basis of these comparisons we found no difference in the growth patterns of the three groups (figure). The weekly increase in these parameters was used to calculate velocity measurements, which showed no significant difference (one way analysis of variance) between the three groups (table 2).

We did not find the skinfold thicknesses a reliable method of assessing growth in these infants of low birth weight as there was marked interobserver variability between the two people responsible for the measurements. We have found a striking similarity in growth rate for all babies irrespective of their individual starting point or method of feeding.



Mean (SD) weight, length, and occipitofrontal circumference (OFC) related to gestational age.

Table 2 Growth velocities mean (SD) values

	Feeding group		
	TP	*cNG*	*bNG*
Weight gain (g/week)	157·6 (59·6)	155·3 (47·6)	167·8 (49·6)
OFC gain (mm/week)	10·62 (2·92)	9·40 (2·32)	9·92 (2·07)
Length gain (mm/week)	11·30 (4·06)	10·41 (4·40)	11·45 (4·56)

TP, transpyloric; cNG, continuous nasogastric; bNG, bolus nasogastric feeding; OFC, occipitofrontal circumference.

The initial biochemical data on entry to the study and on exit at 1600 g are compared in table 3. There was a slight rise in albumin and fall in urea over the period of the study. Similarly, there was a small increase in alkaline phosphatase and fall in transferrin in all groups. When changes between the final and initial value of each subject were analysed (one way analysis of variance), there was no evidence of significant differences between the biochemical results for the three groups. Prealbumin concentrations were not used in assessing the efficacy of the feeding methods because of methodological difficulties. The immunoturbidimetric assay correlated with an immunodiffusion method when initially compared using adult plasma samples. However, there was no correlation when the methods were retrospectively compared using samples from other babies of very low birth weight. Thus the assay results were considered unreliable and not used.

The complications occurring in each group are shown in table 4. The TP group required a total of 31 radiographs in the 10 survivors performed solely for tube positioning. All proved episodes of aspiration occurred when the babies were over 1600 g and were being fed larger volumes less frequently by a bolus nasogastric route. There were two radiographically proved cases of necrotising enterocolitis one each in TP and cNG groups. In the same groups there were two further cases suspected on clinical grounds but not radiologically confirmed and both resolved quickly on antibiotic treatment and short term withdrawal of milk. Four of the 10 babies in the group receiving transpyloric feeding required treatment for gastric bleeding. No infant had gastric bleeding while receiving nasogastric feeding although one infant fed by this method developed bleeding before starting on milk. The high rate of gastric bleeding in the TP group was significant ($p<0.05$ Fisher's exact test).

Table 3 Plasma biochemical concentrations (mean (SD) values)

	Feeding group		
	TP	*cNG*	*bNG*
Transferrin (g/l)			
Initial	1·90 (0·47)	1·82 (0·51)	1·65 (0·35)
Final*	1·65 (0·32)	1·69 (0·61)	1·58 (0·44)
Change	−0·25 (0·64)	−0·13 (0·51)	−0·07 (0·64)
Albumin (g/l)			
Initial	26·8 (3·2)	27·1 (3·6)	25·3 (4·0)
Final*	28·0 (2·0)	30·2 (2·9)	26·3 (3·0)
Change	1·25 (2·6)	3·10 (4·2)	1·00 (4·7)
Alkaline phosphatase (IU/l)			
Initial	547 (193)	569 (269)	499 (247)
Final*	573 (276)	623 (142)	557 (153)
Change	26·00 (290)	53·7 (226)	58·4 (288)
Urea (mmol/l)			
Initial	3·26 (1·66)	3·88 (2·37)	3·72 (2·03)
Final*	1·25 (0·43)	1·39 (0·62)	1·56 (0·71)
Change	−2·01 (1·6)	−2·49 (2·4)	−2·16 (1·9)

TP, transpyloric; cNG, continuous nasogastric; bNG, bolus nasogastric feeding.
*Final figures at exit from study, ie when weight reached 1600 g.

Table 4 Complications in 34 survivors

Complications	*Feeding group*		
	TP (n=10)	*cNG (n=12)*	*bNG (n=12)*
Extra abdominal radiographs	31 (1–9)	0	0
Proved aspiration	2*	1*	0
Necrotising enterocolitis			
Proved	1	1	0
Probable	1	1	0
Septicaemia (*Staphylococcus epidermidis*)	1	1	1
Gastric bleeding	4	0	1†

TP, transpyloric; cNG, continuous nasogastric; bNG, bolus nasogastric feeding.
*After reaching 1600 g.
†Before milk started.

Discussion

Transpyloric feeding is more difficult to initiate than either bolus or continuous nasogastric feeding, and if premature babies are to be fed by this manner some worthwhile benefit has to be demonstrated. Such benefits might be improved growth and nutrition, improved tolerance of feeding, or reduced side effects.

Van Caillie and Powell compared continuous nasogastric feeding with nasoduodenal feeding in infants under 1300 g.[1] They found better growth in the nasoduodenal group related to a higher energy input. Studies by Pereira and Lemons and by Laing *et al*, including larger babies up to 1700 g and 1500 g respectively, found no difference in growth between infants receiving bolus nasogastric feeding and infants receiving nasoduodenal feeding.[2,3] Pereira and Lemons found no difference in total protein levels in their two groups; and our wider range of biochemical data also shows no advantage from transpyloric feeding. The earlier studies[1,2] included few ventilated infants (none and under 50% respectively) while 74% of our 34 survivors were ventilated.

Our results show no nutritional benefit from transpyloric feeding either on the basis of the biochemical measurements or the anthropometric data. Transpyloric feeding requires more radiological exposure and more early handling. It is also associated with a significant incidence of gastric bleeding, although we have not seen this reported before. It seems likely that bypassing the stomach fails to neutralise the gastric acid secreted as a result of gastrin stimulation provoked by the presence of milk in the small bowel.

Our results suggest that the transpyloric route does not have a routine role in feeding preterm infants. There are significant disadvantages and no nutritional benefits. Nasogastric feeding either continuously or by frequent boluses can achieve similar oral energy input and appears both safe and effective. Previous reports of aspiration with nasogastric feeding may be related to inappropriately high volumes being given without monitoring of gastric aspirates. More widespread use of parenteral nutrition now allows a more controlled introduction of nasogastric feeding. We would recommend reserving transpyloric feeding for those infants who persistently fail to tolerate nasogastric feeding.

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Risk factors for necrotising enterocolitis: the influence of gestational age

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Abstract

Over a 7 year study period, 82 infants were identified who had necrotising enterocolitis (NEC). A case-control study of the 74 preterm infants was performed to determine those factors which contributed to the development of NEC. The 35 infants with NEC and gestation between 30–36 weeks, when compared with control infants matched for gestational age, had significantly lower birthweight centiles, cord pH, and 1 minute Apgar scores. By contrast, there were no significant differences between the 39 infants with NEC and controls in the 25–29 week group, except that fewer babies with NEC had received breast milk. The eight term babies all appeared to have an obvious predisposing event. We thus propose a model in which susceptibility to NEC is dependent on gestational age. In the 25–29 week range all babies are at risk on the basis of extreme prematurity. In the 30–36 week range asphyxiated and growth retarded babies are at increased risk, while at term a major predisposing event appears to be required.

Necrotising enterocolitis (NEC) remains a major life threatening disease seen in neonatal intensive care units, and despite investigation by many groups the aetiology of the disease has defied clear explanation. A number of groups have suggested that for preterm infants, prematurity is the only perinatal factor that is related to an increased risk of NEC.[1–5] However, in other reports in which risk factors for NEC were identified, these often differed from study to study. For example, hyaline membrane disease was reportedly more common in patients with NEC,[6–8] or was more common in controls.[1 4] Similarly, in some reports asphyxia[7–10] and umbilical artery catheterisation[6–8 10] were associated with NEC, but were not in others.[1–5 9 11] The most likely explanation for this lack of agreement lies in the differences in patient populations in the studies. Those studies examining the most premature babies (<1500 g,[4 11] <1750 g[3]) tended to report a lack of NEC risk factors, while those which included all newborns up to term tended to report positive findings. Furthermore, there were small numbers of cases of NEC in some studies, different management policies, and the inclusion of varying numbers of outborn babies in some series.

There is mounting evidence that risk factors vary with birth weight or gestational age.[7 9 12] In those studies utilising case-control design, matching for birth weight was most commonly employed.[1 2 5 8 10 11] Such a choice is less than ideal as it fails to take into account the large differences in maturity that occur between small for dates and large for dates babies of similar weight. One study controlled for gestational age, but this was confined to 'late onset' cases of NEC and included only 23 cases.[13]

Recent reports have provided new information on the aetiology of NEC by demonstrating a highly significant association between absent or reversed end diastolic flow velocity waveforms (AREDF) in the umbilical artery or fetal aorta and the subsequent development of NEC.[14 15] For the first time a subgroup of preterm infants has been identified which appears to be at greatly increased risk of developing NEC. Although such infants are on average very growth retarded, Malcolm *et al*, in a case-control study in which infants were matched for gestational age and birth weight, concluded that the risk of NEC was related to the AREDF rather than growth retardation.[14] Nevertheless, one might anticipate an increased incidence of NEC among growth retarded infants, and it is surprising that such an association has not been reported in the many previous studies involving the identification of risk factors for NEC.

We were prompted to undertake a study of NEC at King George V Hospital for Women because of the persisting occurrence of NEC, despite significant advances in other areas of neonatal management. We decided to undertake a case-control study, preferring to control for gestational age for the reasons mentioned above.

Subjects and methods

All newborn infants born between January 1984 and March 1991 who developed NEC were included in this retrospective study. King George V Hospital for Women is a teaching hospital for the University of Sydney with about 4500 deliveries annually. Although mainly drawing upon the surrounding inner city areas, it is also a major referral centre for the in utero transfer of high risk pregnancies, with a large proportion of the babies <32 weeks' gestation (45%) being in this category.

NEC was defined as the presence of clinical features of NEC (bilious aspirates or vomits, abdominal distension, systemic features such as lethargy and apnoea, with or without bloody stools) and radiological features (pneumatosis coli with or without gas in the portal circulation), and/or pathological evidence from laparotomy or necropsy specimens. Pneumoperitoneum

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without pneumatosis was not taken to indicate NEC unless there was unequivocal evidence from pathological specimens, as spontaneous perforation of the gut is a well recognised entity that appears to be distinct from NEC.[16] Using these strict guidelines, 82 cases were identified.

Control infants were selected from the admission book of the neonatal intensive care unit and were defined as the infant born nearest in time and with the same gestational age to that of the infant with NEC. The only grounds for rejecting a control were failure to survive for the number of days equal to age at onset of NEC in the matched infant. In the majority of cases an early ultrasound result was available to confirm the gestational age, which was nominated from the antenatal data on day 1. Birthweight centiles were calculated using standard methods[17] and were derived from birth weight and gestational age data at this hospital over the period of the study.

Most of the data required for this study were obtained from the computerised database of the neonatal intensive care unit, into which data for babies admitted to the nursery had been routinely entered since the beginning of the study period. Cases of NEC were then checked against manual records kept over the study period. Recall of medical records was necessary to obtain details of infant feeding which had not been included in the unit database.

For analysis of matched case-control pairs, SPSS/PC+[18] and EPI-INFO[19] computer statistical programs were employed. McNemar's test was used for comparing dichotomous variables. On testing of continuous variables, only birthweight centile was normally distributed, and paired *t* tests were employed. Wilcoxon's signed ranks test was used for comparison of the other continuous variables.

Results

GENERAL FEATURES

Eighty two cases of NEC were identified over the 87 month study period, representing an incidence of 9·4 cases/year. The mean birth weight was 1418 g (mean birthweight centile 37%) and the mean gestational age 30·4 weeks. There were 23 deaths, giving an overall mortality rate of 28%. The mean gestational age of infants who died was 28 weeks, with the oldest being 34 weeks, whereas the mean for surviving babies was 31 weeks. Overall, 30 babies (37%) underwent surgery of whom 16 (53%) were survivors. Of the blood cultures collected on diagnosis of the NEC, 20 (24%) were positive, with the following pattern: *Klebsiella* spp (n=7), *Staphylococcus epidermidis* (n=6), *Escherichia coli* (n=3), *Clostridium* spp (n=2), *Enterobacter* spp (n=1), and α-haemolytic streptococcus (n=1).

In all cases of NEC the baby had been fed before the onset of symptoms. The age at onset of NEC overall had a mean of 11 days, but with a mode of 5 and median of 9. There was a pattern of early onset NEC with the older babies and late onset NEC with the more premature. There was a significant negative correlation between gestational age and day of onset of NEC ($r=-0{\cdot}35$, $p=0{\cdot}002$), in agreement with previous studies.[2]

The 82 babies included 74 preterm and eight term infants. Because the term babies appeared to have obvious predisposing factors they were analysed separately from the preterm infants.

PRETERM INFANTS

The incidence of NEC in each gestational age category is presented in fig 1. Included in fig 1 is the number of babies with NEC at each gestational age. The mean birthweight centiles for babies with NEC and for controls at each gestational age are presented in fig 2. Overall, the babies with NEC had significantly lower birth weights than the controls ($p<0{\cdot}001$). They were significantly more growth retarded, as evidenced by the lower mean birthweight centiles ($p<0{\cdot}001$), or the higher proportion of infants less than the 10th centile ($p=0{\cdot}01$, odds ratio (OR) 3·6, 95% confidence interval (CI) 1·3 to 9·7).

INFANTS <30 WEEKS' GESTATION

The differences between NEC and controls for birthweight centile were most noticeable for infants of 30–36 weeks' gestation, whereas in those of 25–29 weeks the corresponding differences appeared to be less significant. In order to highlight this important result, analysis was performed separately for babies of 25–29 and 30–36 weeks' gestation. The results for the 39 cases in the 25–29 week group are presented in table 1.

The striking result that emerged was the lack of identifiable risk factors in this age category,

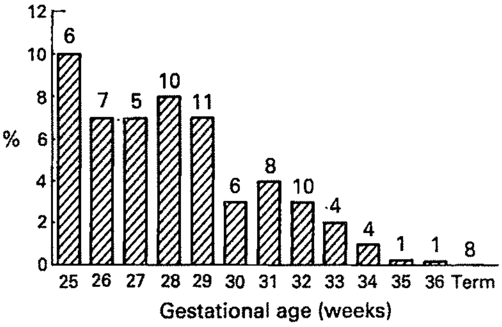

Figure 1 Incidence (%) of NEC by gestational age, including total number with NEC at each gestational age.

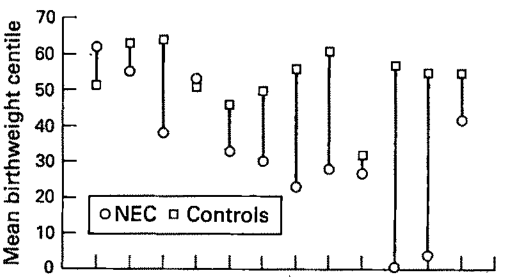

Figure 2 Mean birthweight centiles for babies with NEC and for controls.

apart from increased mortality in the NEC infants. However, factors that did reach significance were the higher proportion of babies who received infant formula alone in the NEC group (p=0·04, OR=4·0, CI=1·1 to 14·1), and the lower proportion of babies who received only expressed breast milk in the NEC group (p=0·03, OR=0·29, CI=0·09 to 0·87).

INFANTS 30–36 WEEKS' GESTATION

The results for the 35 infants in this category together with their controls is presented in table 2. The birth weights and birthweight centiles for the babies with NEC were significantly lower than the controls (p<0·001) and there was an appreciable increase in the proportion of babies with NEC with significant growth retardation (<10th centile: p=0·02, OR=6·0, CI=1·3 to 26·8; <3rd centile: p=0·03, OR=9·0, CI=1·1 to 71·0). In contrast to the group of 25–29 weeks' gestation, babies with NEC in this group when compared with controls had significantly lower arterial cord pH (p=0·05) and Apgar scores at 1 minute (p=0·04, OR=5·0, CI=1·1 to 22·8), but did not show a significant difference with regard to feeds.

Table 1 Comparison of clinical variables in case-control matched pairs 25–29 weeks' gestation. Results are given as percentages of babies with factor present or as means for continuous variables

Clinical variable	*NEC*	*Controls*	*Comparison**
Birth weight (g)	1013	1052	38·5 (51·1)
Birthweight centile	47	53	6·2 (7·3)
<10th Centile (%)	15	8	2·0 (0·5 to 8·0)
<3rd Centile (%)	5	5	1·0 (0·14 to 7·1)
Male sex (%)	39	41	0·9 (0·34 to 2·3)
Pre-eclampsia (%)	28	15	2·0 (0·7 to 5·8)
Antepartum haemorrhage (%)	31	21	1·6 (0·6 to 4·1)
Intrauterine infection (%)	39	49	0·8 (0·3 to 2·1)
Prolonged rupture of membranes (%)	36	49	0·6 (0·2 to 1·5)
Antenatal steroids (%)	72	80	0·7 (0·2 to 1·8)
Caesarean section (%)	54	36	2·0 (0·8 to 5·0)
Cord arterial pH	7·21	7·23	0·02 (0·03)
Apgar score (%):			
1 Min <4	39	33	1·3 (0·5 to 3·2)
5 Min <7	33	23	1·8 (0·6 to 5·4)
Hyaline membrane disease (%)	67	44	2·5 (0·97 to 6·4)
Pneumothorax (%)	15	26	0·6 (0·2 to 1·7)
Patent ductus arteriosus (%)	41	39	1·1 (0·4 to 3·2)
Umbilical artery catheter (%)	33	18	3·0 (0·8 to 11·1)
Maximum serum bilirubin (µmol/l)	205	216	11·4 (10·8)
Maximum serum creatinine (µmol/l)	130	125	4·2 (7·9)
Day 1 packed cell volume	0·45	0·45	0·0 (0·02)
First feed (days)	4·7	4·5	0·26 (0·38)
Formula only (%)	39	15	4·0 (1·1 to 14·1)†
Expressed breast milk only (%)	13	39	0·3 (0·1 to 0·9)‡
Mortality (%)	41	5	15·0 (2·0 to 113·6)§

*For continuous variables the mean difference and standard error are presented and for dichotomous variables the odds ratio and 95% confidence intervals are given. p Values were obtained using McNemar's test for the dichotomous variables, paired *t* test for birthweight centile data, and Wilcoxon rank sign test for other continuous variables.
†p=0·04, ‡p=0·03, §p=0·001.

Table 2 Comparison of clinical variables in 35 case-control matched pairs of infants 30–36 weeks' gestation. Results given as percentage of babies with factor present or as means for continuous variables

Clinical variable	*NEC*	*Controls*	*Comparison**
Birth weight (g)	1479	1869	390 (84·7)†
Birthweight centile	24	54	30 (5·8)‡
<10th Centile (%)	37	9	6·0 (1·3 to 26·8)§
<3rd Centile (%)	29	6	9·0 (1·1 to 71·0)¶
Male sex (%)	60	43	1·9 (0·7 to 4·7)
Pre-eclampsia (%)	34	29	1·4 (0·5 to 3·8)
Antepartum haemorrhage (%)	17	23	0·8 (0·3 to 2·2)
Intrauterine infection (%)	11	14	0·8 (0·2 to 3·0)
Prolonged rupture of membranes (%)	6	14	0·4 (0·1 to 2·1)
Antenatal steroids (%)	66	57	1·4 (0·5 to 3·8)
Caesarean section (%)	77	54	2·6 (0·9 to 7·3)
Cord arterial pH	7·21	7·24	0·04 (0·02)‖
Apgar score (%):			
1 Min <4	31	9	5·0 (1·1 to 22·8)**
5 Min <7	20	6	3·5 (0·7 to 16·8)
Hyaline membrane disease (%)	43	26	2·2 (0·8 to 6·3)
Pneumothorax (%)	6	11	0·3 (0·03 to 3·2)
Patent ductus arteriosus (%)	9	3	3·0 (0·3 to 28·8)
Umbilical artery catheter (%)	11	6	2·0 (0·4 to 10·9)
Maximum serum bilirubin (µmol/l)	225	246	19·3 (15·7)
Maximum serum creatinine (µmol/l)	112	109	6·1 (8·9)
Day 1 packed cell volume	0·49	0·52	0·04 (0·03)
First feed (days)	3·1	2·5	0·6 (0·5)
Formula only (%)	46	34	1·2 (0·4 to 3·9)
Expressed breast milk only (%)	17	14	1·8 (0·6 to 5·4)
Mortality (%)	20	0	—††

*For continuous variables the mean difference and standard error is given and for dichotomous variables the odds ratio and 95% confidence intervals are presented. p Values were obtained using McNemar's test for the dichotomous variables, paired *t* test for birthweight centile data, and Wilcoxon rank sign test for other continuous variables.
†p<0·001, ‡p<0·001, §p=0·002, ¶p=0·03, ‖p=0·05, **p=0·04, ††p=0·02.

TERM INFANTS

The eight term infants who developed NEC had a mean (SD) birth weight of 3121 (469) g, mean birthweight centile of 46 (33), and gestational age of 38 (1) weeks. In four the onset of NEC followed shortly after an exchange transfusion (three via an umbilical venous catheter and one via peripheral lines) and were previously well term infants. In two, there was profound birth asphyxia (cord pH 6·96 and 6·97) while in the seventh the baby was shocked at birth due to fetomaternal transfusion, with an initial packed cell volume of 0·15. In the eighth the mother abused multiple drugs including heroin and cocaine, and the baby was polycythaemic and hypoglycaemic after delivery.

GROUP WITH SPONTANEOUS PERFORATION

There were six infants who developed pneumoperitoneum, but who had neither pneumotosis on radiography nor pathological findings on laparotomy or postmortem specimens consistent with NEC, and were therefore excluded as cases of NEC. They were more immature than the babies with NEC (mean gestational age 26 (2) weeks). Two of the six were never fed and only one had birth asphyxia. The presumed mechanism in these cases is perforation in an area of focal ischaemia,[16] perhaps due to emboli.

Discussion

This study includes one of the largest group of babies with NEC that have been analysed using a matched case-control design. It also has the advantage that the babies were all managed in a single nursery from birth. Matching for gestational age has allowed insights into NEC that have been difficult to appreciate in previous studies matching for birth weight or with no matching at all. The results show a definite pattern of changing risk factors dependent on the gestational age. The principal factor is prematurity itself, as demonstrated in fig 1 where the incidence was 10% for 25 week infants, falling to 0·03% at term.

The group with gestational age of 25–29 weeks is notable for the lack of identifiable risk factors. An elegant model to possibly explain the occurrence of NEC in this group of infants has been proposed by Clark and Miller.[20] Their model involves the pathological interaction of milk constituents and bacteria on the distal gut mucosa, and is independent of perinatal risk factors. The only perinatal factor that was related significantly to the incidence of NEC was whether or not the infant was given expressed breast milk. Our finding of a protective effect of expressed breast milk is in agreement with the recent report of Lucas and Cole.[6] Such a protective effect may have been missed in previous studies because of small numbers of babies who received breast milk, or failure to control for gestational age. For example, in two studies the babies receiving expressed breast milk had a lower mean gestational age than those who received formula.[21 22] Hence, as can be seen from fig 1, they would be expected to have an increased incidence of NEC that may have offset any improvement due to the expressed breast milk. The finding of a protective effect caused by the expressed breast milk is further supported by the prospective study of Eibl *et al* in which an oral immunoglobulin A/immunoglobulin G mixture was found to significantly reduce the incidence of NEC.[23]

It can be seen from table 2 that babies with NEC in the 30–36 week range are significantly more growth retarded than controls, and had a higher incidence of asphyxia, as evidenced by lower 1 minute Apgar scores and cord pH. There were no other significant differences. The recent reports of an association between AREDF in the fetal umbilical artery or aorta and the subsequent development of NEC raises the questions of whether the association between NEC and growth retardation found in this study is primary, or secondary to a high proportion of these infants having AREDF. As Doppler flow studies have been performed only on selected fetuses during the last two years at this hospital, there are not enough data at present to address this question.

It is interesting that a significant association between NEC and growth retardation was not reported in the study of Stoll *et al* who reported 46% of their babies with NEC to be small for gestational age (SGA).[5] However, 38% of their controls, matched for birth weight, were also reported as being SGA, and comparison of these groups failed to yield growth retardation as a significant difference. Similarly, the association was not reported by Kleigman *et al* despite the fact that 27% of their cases of NEC were below the 3rd centile.[4] However, by choosing babies of <1500 g, a control population resulted which included an excess of SGA babies at the higher gestations, and 22% of the 553 babies without NEC were less than the 3rd centile. As a consequence, comparison of these two populations again failed to yield growth retardation as a risk factor.

NEC in term babies is a rare event (0·03% incidence in this series). The eight babies described here had well defined events that could compromise the gut in each case. The findings of a relationship between NEC and exchange transfusion, asphyxia, shock, or polycythaemia in more mature babies is well recognised.[9 24–28] It is difficult not to implicate ischaemia in the pathogenesis of NEC in this group.

In summary, our results support a model of NEC in which susceptibility to NEC is inversely related to gestational age. Term infants have relatively mature gastrointestinal and immune systems, and require a significant insult before NEC can develop, whereas in babies <30 weeks' gestation NEC occurs most commonly in the absence of a well defined insult, the primary risk being gut immaturity itself. Between 30 weeks and term, factors such as growth retardation and asphyxia become increasingly significant. We conclude that babies at risk of NEC include all babies <30 weeks, all growth retarded babies (especially those with AREDF), and term babies with severe asphyxia, shock, exchange transfusion, or polycythaemia. Our findings also support the view that breast milk is associated with a reduced risk of NEC, especially in babies of 25–29 weeks' gestation.

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Capillary plasma elastase α_1-proteinase inhibitor in infected and non-infected neonates

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Abstract

Capillary heel prick plasma elastase α_1-proteinase inhibitor (Eα_1-PI) measured by an immunoassay (using commercially available reagents) was examined as an early indicator of neonatal sepsis. Fifty five infants were studied within 24 hours of birth; 60 (including 10 studied on the first day of life) were examined between two and 30 days after birth. Reference ranges for the neonatal period were developed. Raised Eα_1-PI concentrations (range 440–2600 μg/l) were found at the outset of each of the 24 infectious episodes including five with concomitant neutropenia. On the first day of life, obstetric and neonatal complications were also associated with high concentrations (range 190–2400 μg/ml). In infants who survived infection, Eα_1-PI normalised with antibiotic treatment. It is concluded that capillary heel prick plasma is suitable for Eα_1-PI testing and raised concentrations provide a sensitive but non-specific index of infection in the first 24 hours after birth. Sequential testing may provide early warning of infectious complications and serve as a guide to the cessation of antibiotic treatment.

Recent studies in both adults[1–3] and neonates[4–6] indicate that raised venous plasma elastase α_1-proteinase inhibitor (Eα_1-PI) complex concentrations provide a sensitive indicator of systemic bacterial infections. Furthermore, Eα_1-PI appears to correlate with both the severity of inflammation and the degree of illness.[1 2] The Eα_1-PI complex appears in plasma after tissue injury: elastase is released into the circulation as activated polymorphonuclear leucocytes (PMN) degranulate.[7] The elastase is subsequently inactivated and complexed predominantly by α_1-proteinase inhibitor (α_1-PI) and to a lesser degree by α_2-macroglobulin.[8]

In many neonatal intensive care units, capillary blood samples obtained by heel prick puncture are used for serial monitoring of haematological and biochemical indices. In the present study we assessed the suitability of capillary heel prick plasma for Eα_1-PI testing and examined the role of Eα_1-PI in the early diagnosis and monitoring of neonatal infections.

Patients and methods

The infants studied were drawn from the neonatal population of the Mater Mothers' Hospital, South Brisbane, Australia. The study was approved by the Mater Mothers' Hospital ethics committee. Informed parental consent was not considered necessary as testing was performed on residual plasma from blood samples submitted to the clinical laboratory for haematological studies. The study population included infants from two age groups. Group 1 comprised infants examined within 24 hours of birth who were undergoing a sepsis screen because of the presence of predisposing factors including prematurity, prolonged rupture of membranes, and maternal complications such as hypertension or instrumental birth. Group 2 comprised infants studied two to 30 days after birth in whom there was a clinical suspicion of infection or who were undergoing full blood count testing to monitor their clinical progress and as a screening test for sepsis. Group 1 (n=55) included 33 preterm infants with mean (SD) gestational age 30·2 (3·1) weeks (range 25–36 weeks) and 22 term infants with mean gestational age 39·4 (0·6) weeks (range 37–41); group 2 (n=60) included 10 group 1 infants. Infants were enrolled in the study if: (i) a capillary heel prick sample was submitted; (ii) there was sufficient residual plasma for Eα_1-PI testing; and (iii) separation of plasma was performed within two hours of collection.

Maternal and infant patient records and postmortem reports were reviewed and clinical, radiological, microbiological, and haematological data collected. Infants were classified as proved, probable, or possible infection and as non-infected. The non-infected group was subdivided into those with a non-eventful clinical course and those with obstetric or neonatal complications. Infants with positive blood cultures (performed according to standard techniques by the clinical laboratory) and a clinical course consistent with sepsis were classified as proved infection. The 'time of onset' of infection was designated as the earliest finding of either the clinical onset of infection or the time of collection of the blood culture which subsequently proved positive. Causative organisms in the group 1 infants (n=7) with proved infection were: group B streptococcus (n=2), *Escherichia coli* (n=3), *Bacteroides fragilis* (n=1), and *Serratia marcescens* (n=1). Causative organisms in four of the seven group 2 infants with nine infectious episodes were: *Staphylococcus epidermidis* (n=1), *Streptococcus viridans* (n=1), *Candida albicans* (n=1), and *S marcescens* (n=1); there were five episodes of necrotising enterocolitis. Criteria for probable infection (n=9, group 1) were negative blood cultures but strong clinical (and in some cases radiological) evidence of infection associated with intrapartum antibiotic treatment. Criteria for possible infection (n=4, group 1)

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were: maternal clinical and histological chorioamnionitis, intrapartum antibiotic therapy, asymptomatic infant given antibiotic cover, negative blood cultures, and haematological changes suggestive of infection. All other infants were considered non-infected.

Blood samples (approximately 300 to 400 μl) were collected by heel prick puncture into tubes anticoagulated with EDTA (Microtainer, Becton Dickinson). After haematological testing, the plasma was separated and stored at −70°C until testing. The time of collection of blood and separation of plasma was recorded. Specimens not separated within two hours of collection were discarded as $E\alpha_1$-PI concentrations rise if separation is delayed beyond two hours.[9]

ASSAY[10]

Duplicate testing was performed (without knowledge of the infection status of the infants) using a commercially available solid phase enzyme linked immunoassy kit (E Merck). The two hour test procedure was modified slightly to provide a micromethod using only 10 μl of plasma per test. According to the method principle, standard and plasma samples were exposed sequentially (with incubation and washing steps between) to an elastase antibody and an alkaline phosphatase labelled antibody to $E\alpha_1$-PI which attach to the elastase and $E\alpha_1$-PI antigenic determinants respectively. To reduce the plasma volume required for the test, a Gilson Dilugil V dilutor (Gilson Medical Electronics) was used to dilute 10 μl of the plasma samples directly with 490 μl of diluent into the elastase antibody labelled tubes. Colour development of plasma samples from a 4-nitro phenylphosphate substrate was compared with results of a standard curve.

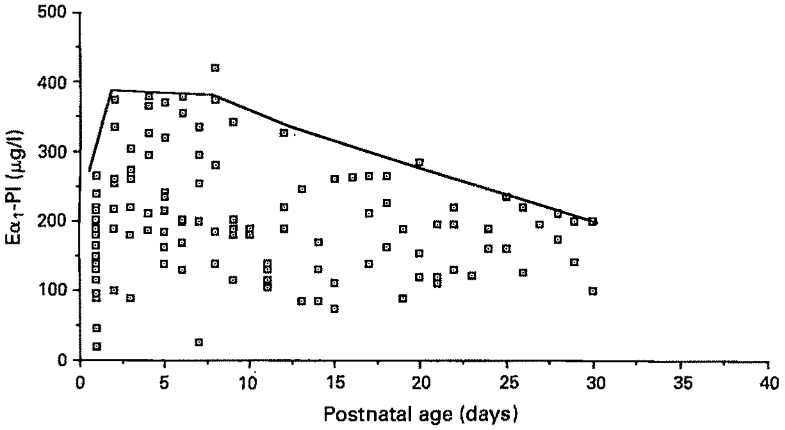

Figure 1 Reference ranges for capillary heel prick plasma concentrations of $E\alpha_1$-PI in the first 30 days after birth.

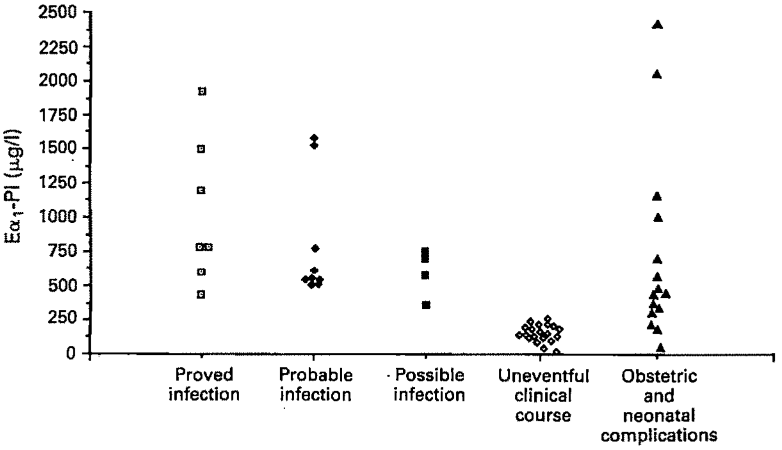

Figure 2 Capillary heel prick plasma concentrations of $E\alpha_1$-PI in the first 24 hours after birth in infants with proved (n=7), probable (n=9), or possible (n=4) infection, an uneventful clinical course (n=22), and obstetric and neonatal complications (n=15).

Results

Reference ranges for $E\alpha_1$-PI for the first 30 days of life (fig 1) were determined from 20 group 1 non-infected infants with an uneventful perinatal and postnatal course and 102 determinations on 53 healthy group 2 infants. Because of the restricted number of estimations in some time frames, preliminary bounds were drawn by visual inspection using the non-parametric method employed by Speer *et al*.[4] The maximum concentration on the first day of life was 265 μg/l and there was a postnatal rise on day 2 to a maximum of 375 μg/l which persisted till day 8. Thereafter, the maximum value decreased (342 μg/l between days 9 and 20; 235 μg/l between days 21 and 30) until 30 days when a stable value of 200 μg/l was found (a further 40 estimations were performed on 25 infants between 31 and 60 days after birth who were less than 40 weeks' adjusted gestational age and the range of values was 75 to 225 μg/l with 95% of values ≤200 μg/l; data not shown).

Figure 2 shows the distribution of $E\alpha_1$-PI concentrations in 55 group 1 infants. All infants with proved (n=7) or probable (n=9) infection had $E\alpha_1$-PI concentrations greater than 440 μg/l including four infants with proved infection who were neutropenic (according to the reference ranges of Manroe *et al*[11]) at the time of testing. Two of the four neutropenic infants died: initial PMN count and $E\alpha_1$-PI concentrations were $0{\cdot}15\times10^9$/l and 780 μg/l respectively for one infant with *E coli* septicaemia and $1{\cdot}9\times10^9$/l and 580 μg/l respectively for the other infant with group B streptococcal septicaemia. Corresponding values for PMN count and $E\alpha_1$-PI concentrations for the two survivors were $0{\cdot}8\times10^9$/l and 600 μg/l (*E coli* septicaemia) and $0{\cdot}24\times10^9$/l and 440 μg/l (group B streptococcal septicaemia). Four infants with possible infection had values ranging from 360 to 750 μg/l. Both obstetric and neonatal complications were associated with increased $E\alpha_1$-PI concentrations. Grossly raised concentrations were found for two of three non-infected infants with severe intrapartum hypoxia (1000 and 2400 μg/l), one infant with clinically and virologically proved cytomegalovirus embryopathy (1150 μg/l), and one infant with ABO haemolytic disease (1000 μg/l). Raised concentrations (range 305–700 μg/l) were also found for five of seven infants of mothers with pregnancy induced hypertension and two of three infants with retained fetal lung fluid.

In group 2 infants, clear delineation between infected (nine infectious episodes) and non-infected infants was obtained (fig 3) including one infant with necrotising enterocolitis who was neutropenic at the time of testing. Another infant (with *S epidermidis* septicaemia) had a raised concentration (1000 μg/l) 24 hours before clinical onset of disease. Only one non-infected healthy infant had an unexplained raised Eα_1-PI concentration (1200 μg/l).

The results of sequential testing performed on four infected group 1 infants who survived infection is shown in fig 4. The concentrations of Eα_1-PI normalised with response to antibiotic treatment and recovery from infection. Case 1 was an infant with probable intrauterine infection (radiological evidence of pneumonia) born after seven day rupture of maternal membranes who developed a leukaemioid blood picture (PMN count of 31·8×10^9/l and Eα_1-PI value of 1500 μg/l at birth, rising to a zenith on the third day after birth of 65·8×10^9/l (Eα_1-PI 4000 μg/l) with normalisation (3·3×10^9/l and 200 μg/l respectively) 27 days after birth. Case 2 had septicaemia and pneumonia due to *E coli* with severe neutropenia (PMN count <0·1×10^9/l) at birth with an Eα_1-PI of 440 μg/l. Adjunctive treatment included a granulocyte transfusion eight hours after birth and intravenous immunoglobulin (Sandoglobulin) for five days. The infant developed a leukaemoid blood picture with the PMN count reaching a zenith of 58×10^9/l eight days after birth (Eα_1-PI 600 μg/l); the Eα_1-PI normalised (125 μg/l) 10 days after birth with clinical recovery but the PMN count remained high until 20 days after birth. Cases 3 and 4 had uncomplicated septicaemia due to *S marcescens* and *B fragilis* respectively.

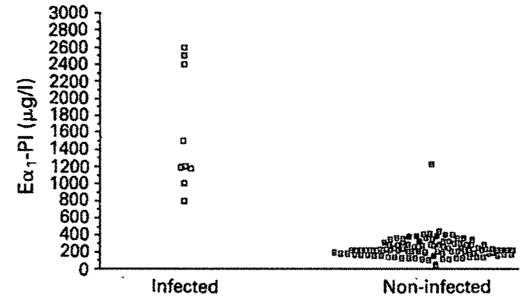

Figure 3 Results of 102 determinations of capillary heel prick plasma Eα_1-PI concentrations in infected (nine infectious episodes) and non-infected infants between two and 30 days after birth.

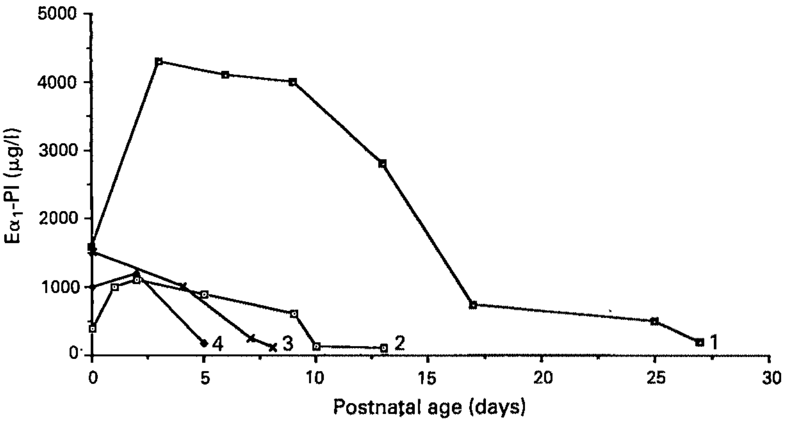

Figure 4 Sequential capillary plasma Eα_1-PI concentrations in four infants with early onset sepsis who survived. Case 1 had probable infection with a leukaemoid blood picture; case 2 had E coli septicaemia and pneumonia and was neutropenic at birth; and cases 3 and 4 had uncomplicated septicaemia due to S marcescens and B fragilis respectively.

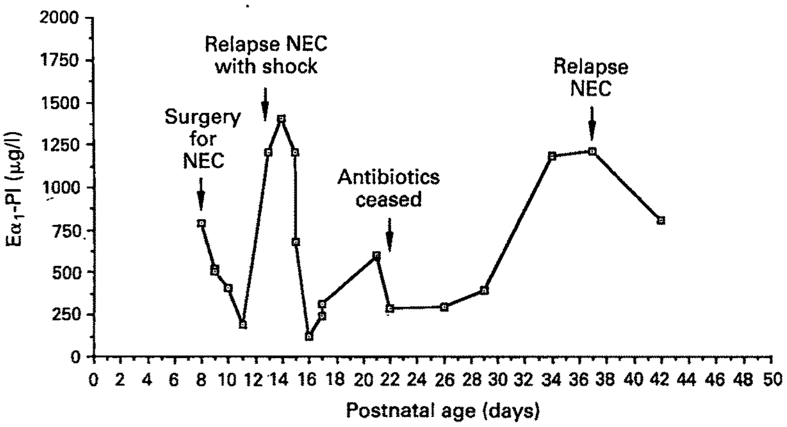

Figure 5 Serial Eα_1-PI data in an infant transferred to our unit eight days after birth with severe neutropenia and extensive necrotising enterocolitis (NEC) involving both small and large bowel and who required surgery for perforation. Subsequently, the infant had a complicated and protracted course with relapses of NEC 13 and 38 days after birth.

Figure 5 displays the results of sequential Eα_1-PI measurements in one infant who was tested longitudinally. The infant who was neutropenic at the time of initial testing was transferred to our unit eight days after birth with necrotising enterocolitis and a perforated bowel requiring resection. The infant had a protracted and complicated clinical course with two relapses of necrotising enterocolitis during the period of testing. The Eα_1-PI concentrations fluctuated with changes in the infant's clinical progress.

Discussion

Our findings indicate capillary heel prick plasma is suitable for Eα_1-PI testing with the present methodology and indicates this complex is a sensitive but non-specific indicator of infection. A microtechnique using capillary plasma is advantageous, particularly in the preterm infant in whom blood sampling should be minimised. With capillary plasma, falsely raised Eα_1-PI values (due to in vitro release of elastase from PMN) could be obtained if difficulty was experienced in collection of the sample or the plasma was contaminated with PMN at the time of separation. However, although no comparative data are available for reference ranges for capillary plasma, our results are in general agreement with the published reference range for venous plasma.[4–6] Capillary plasma Eα_1-PI concentrations were only slightly higher at corresponding postnatal ages than venous plasma (maximum values on day 2 of 375 μg/l compared with 275 μg/l; maximum stable value at 4 weeks of 200 μg/l compared with 190 μg/l between 5 weeks and 14 years of age). The higher Eα_1-PI values in capillary samples may be due to the higher leucocyte counts in the latter samples when compared with venous and arterial samples[12] as Speer *et al* found Eα_1-PI values and the total white blood cell count are positively correlated.[4]

Examination of Eα_1-PI concentrations in the first 24 hours of life may provide a valuable adjunct to the early diagnosis of sepsis in at risk infants. In the present study all infants with proved, probable, or possible infection had raised Eα_1-PI values including four infants who were neutropenic at the time of testing. Raised Eα_1-PI values may assist in earlier identification of the latter group in whom the mortality may be high[13] and may also prove useful in the assessment of clinically well infants whose mothers received intrapartum antibiotic treatment. Our findings in neutropenic infected infants confirm previous reports in neonates and children.[4-6] However, these data should be interpreted with caution in other clinical groups as normal Eα_1-PI values have been reported in infected patients with neutropenia secondary to chemotherapy induced myelosuppression.[14-15] A recent report indicates intracellular elastase concentrations decrease commensurate with chemotherapy.[15] Thus the efficiency of Eα_1-PI as an indicator of infection in neutropenic patients may depend on both an adequate intracellular elastase concentration and/or an adequate marrow myeloid pool. In the present study, both obstetric and neonatal complications including pregnancy induced hypertension, maternal chorioamnionitis, intrapartum hypoxia, retained fetal lung fluid, cytomegalovirus embryopathy, and ABO haemolytic disease were also associated with high Eα_1-PI values. Our findings are in accord with previous reports that found raised Eα_1-PI concentration with several non-infectious factors including meconium aspiration, severe prolonged acidosis, and persistent fetal circulation.[4-6] To date, all tests used to screen for sepsis on the first day of life including gastric aspirate microscopy,[16] neutrophil profiles,[11 17 18] the haematological scoring system,[18] erythrocyte sedimentation rate,[19] and C reactive protein[17 20] have been limited in their usefulness by their non-specificity.

After the first day of life clear delineation between infected and non-infected infants for Eα_1-PI concentrations was obtained. In one infant, with *S epidermidis* septicaemia, the Eα_1-PI concentrations rose 24 hours before the clinical onset of disease. Sequential testing was performed on a small number of infected infants and appears of value in monitoring disease and response to treatment. In infants who survived infection the Eα_1-PI concentrations normalised with antibiotic treatment, and in one infant with necrotising enterocolitis serial monitoring showed Eα_1-PI values fluctuated in parallel with changes in the infant's clinical condition. These findings corroborate the studies by Speer *et al.*[4-6]

We conclude that capillary plasma Eα_1-PI testing provides a valuable adjunct to the early diagnosis of neonatal sepsis. Sequential testing may provide early warning of infectious complications, serve as a guide to cessation of antibiotic treatment in infected infants, and prove useful in monitoring the clinical progress of infants with necrotising enterocolitis.

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Breathing pattern abnormalities in full term asphyxiated newborn infants

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Abstract

Perinatal asphyxia is a cause of significant morbidity among full term infants, but breathing abnormalities after an asphyxic insult have not been studied. This report details breathing patterns of 16 full term asphyxiated infants, during the first week of life who were studied by transthoracic impedance pneumocardiograms. Pneumocardiograms were abnormal in 69% of infants in the asphyxiated group and 13% of infants in the control group. Significant differences were noted in the incidence of prolonged apnoea, the percentage of periodic breathing, and in apnoea density. These results indicate that there are significant abnormalities in the breathing pattern of full term infants, during their first week, after perinatal asphyxia. Similar abnormalities have been described in infants who had experienced 'near miss' sudden infant death syndrome.

Perinatal asphyxia is a cause of significant morbidity among full term infants. Among the central nervous system manifestations, hypoxic-ischaemic encephalopathy is the major event that leads to clinical symptoms including seizures.[1] Many affected infants develop respiratory failure requiring artificial ventilation for a few days. Whether the respiratory failure is due to the direct effect of asphyxia on the respiratory center or to a global suppression of neuronal activity from severe hypoxic-ischaemic encephalopathy is not certain. We have observed several episodes of apnoea not associated with (electroencephalography proved) seizures in full term newborn infants during the postasphyxial state in the nursery. As the breathing pattern of full term neonates who suffered perinatal asphyxia has not been studied in the past, the objective was to study their breathing. Significant abnormalities in the breathing patterns of these full term asphyxiated newborns was found and the findings reported here. As similar abnormalities in breathing are seen in infants who had nearly experienced sudden infant death syndrome ('near miss' SIDS), hypoxia may possibly be the common initiating event responsible for such abnormalities.

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Materials and methods

Sixteen full term infants of appropriate size for gestational age and with a history of perinatal asphyxia were studied. Asphyxia was defined as an Apgar score of 4 or less at 5 minutes after birth and an arterial pH of less than 7·24 with a base deficit in excess of −10 within 30 minutes after birth. Infants with clinical seizures were excluded from the study. Infants with congenital anomalies, congenital infections, and clinically proved early onset sepsis were excluded from the study. The mean (SD) birth weight was 3365 (260) g at a gestational age of 40 weeks (range 38–42 weeks). There were 10 boys and six girls. Sixteen randomly selected full term neonates, also of appropriate size for gestational age, served as controls (eight boys and eight girls). Their mean Apgar score at 5 minutes was 9·4 (range 9–10), and their mean (SD) birth weight was 3310 (315) g at a gestational age of 39·9 weeks (range 38–42).

Twelve hour nocturnal transthoracic impedance pneumocardiograms were obtained between 3 and 7 days of age. These recordings were made on a cassette tape which was subsequently analysed on a computer. The computer software is programmed to report the following variables: apnoea duration of greater than 15 seconds, of 11–15 seconds, or greater than 5 seconds; apnoea density; percentage of periodic breathing; bradycardia; and disorganised breathing.

Apnoea density (A6/D%) is defined as the total duration of apnoeic episodes of 6 seconds or longer divided by total sleep time and multiplied by 100. Bradycardia is defined as heart rate of less than 80 per minute lasting 5 or more seconds. Periodic breathing is defined as three or more apnoeic spells of 3 seconds or longer interrupted by 20 seconds or less of normal breathing without apnoea; the total duration of periodic breathing is expressed as a percentage of total sleep time. Disorganised breathing is defined as short apnoeic episodes accompanied by bradycardia during sleep. Scoring of the pneumocardiogram was carried out by a computer equipped with software programmed to generate a report (Medical Graphics).[2]

The following criteria were used to define normal pneumocardiogram results. A pneumocardiogram is considered normal if there are no episodes of prolonged apnoea (apnoea lasting longer than 15 seconds in duration), apnoea density is less than 0·9, and periodic breathing is less than 3·5% and there are no episodes of bradycardia nor disorganised breathing. These criteria have been published by others.[3–7] All pneumocardiograms recorded on cassette tapes were analysed the next morning to generate hard copy at a recorder speed of 2·4 seconds/mm of paper. Pneumocardiograms were done at a mean postnatal age of 4·06 days (range 3–6) in the control group and 5 days (range 4–7) in the asphyxiated group. Statistical analyses were carried out by two tailed *t* tests for individual

Breathing patterns of infants with asphyxia compared with those of controls

	Asphyxia	*Control*	*p Value*
Mean (SD) birth weight (g)	3365 (260)	3310 (315)	NS
No (%) of infants with prolonged apnoea	5 (31)	0	<0·05
Mean (SD) apnoea density	1·41 (0·87)	0·59 (0·26)	<0·05
Mean (SD) % periodic breathing	3·12 (0·8)	2·13 (0·67)	<0·05
No (%) with normal pneumogram	5 (31)	14 (88)	<0·05

variables between the two groups and χ^2 test with Yates's correction.

Results

Eleven infants (69%) in the asphyxia group had abnormal pneumocardiogram results and five infants had normal results. Only two of the 16 infants in the control group had abnormal pneumocardiogram results ($p<0·05$). Among infants with abnormal pneumocardiograms, five out of 11 (45%) had prolonged apnoea (>15 s); nine out of 11 (82%) had increased apnoea density and six out of 11 (55%) had abnormal periodic breathing. The two abnormal pneumocardiograms in the control group were due to increased apnoea density, with other parameters being normal. We did not analyse the episodes of apnoea 11–15 seconds' duration and episodes of periodic breathing per 100 minutes of sleep time. There were no episodes of isolated bradycardia or disorganised breathing in either group. The abnormalities in the breathing pattern seen among the asphyxiated group were significant ($p<0·05$) when compared with the control group in the following variables: prolonged apnoea, percentage of periodic breathing, and apnoea density (see table).

Discussion

Breathing patterns of full term asphyxiated newborn infants have not been studied in the past. Our results indicate that the breathing patterns are abnormal among asphyxiated infants during the first week of life, but whether these changes are induced by the asphyxia is not known. It had been reported that apnoea in newborn infants is associated with a history of antecedent hypoxia.[8] Infants who had near miss SIDS were reported to have abnormal breathing patterns identified by pneumograms.[3 4 9–11] The abnormalities described in those infants are similar to those which we detected in our group of asphyxiated neonates. There is no information on the breathing pattern of these infants preceding an asphyxial insult. If an hypoxic insult to the brain produced these abnormalities in breathing patterns, then the abnormalities reported in the past in these near miss SIDS infants might also be due to the hypoxic events. If so, then the assessment of breathing patterns should have no predictive value for SIDS, as the hypoxia may be an acute event immediately preceding death. However, the assessment of breathing patterns offers an added tool in evaluating the severity of (or effect of) asphyxia on central respiratory centre.

Pneumocardiograms have been used as a tool in assessing breathing patterns in infants with apnoea of prematurity, apnoea of infancy, near miss SIDS, infants on home apnoea monitors, siblings of SIDS infants, and those born to mothers practising substance abuse during pregnancy.[3 9 10 12–14] The predictive value of pneumocardiograms in SIDS is very controversial.[15–17] Several variables in the pneumocardiograms can be analysed. We chose to use prolonged apnoea, percentage of periodic breathing, apnoea density, bradycardia, and disorganised breathing as the variables in the study of breathing pattern. All pneumocardiograms in this study were recorded in the hospital. As computer aided pneumogram scoring and interpretation reduce the interpersonal bias involved in the reports, we employed this technique.[2 18]

None of our non-asphyxiated (control group) infants had prolonged apnoea. This is similar to the reported findings of Kelly *et al.*[4] The increased apnoea density noted in two infants in the control group was due to multiple episodes of apnoea of 6–14 seconds' duration. None of the infants in either group had obstructive apnoea. The reliability of detection of obstructive apnoea from pneumocardiogram tracings is debatable. Bradycardia is a usual accompaniment of obstructive apnoea and as we could not detect any episodes of bradycardia with chest wall movement, we made the assumption that there were no obstructive apnoea spells. All our infants were breathing spontaneously in room air when we studied them. There were no episodes of cyanosis in any of our infants. We did not monitor the infants with an oximeter to record oxygen saturation continuously during the study.

It is known that preterm infants increased periodicity in the breathing pattern and this is abolished by oxygen administration.[19] If periodic breathing and subsequent apnoea are due to mild hypoxia in preterm infants, the effects of acute hypoxia and acidosis as seen in perinatal asphyxia may last several days. It is possible that the observed changes in the breathing pattern of these infants may be due to that; but our infants were full term and such changes have not been described in the past. In conclusion, we have identified abnormalities in the breathing pattern of full term asphyxiated newborn infants during the first week of life. The duration of the persistence of these abnormalities in the breathing pattern needs further studies in future.

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Intracardiac thrombus formation with rapidly progressive heart failure in the neonate: treatment with tissue type plasminogen activator

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Abstract
A newborn is described in whom the use of a central venous line was complicated by septicaemia and by intracardiac thrombus formation with tricuspid valve insufficiency and heart failure. Besides antibiotics, treatment consisted of tissue type plasminogen activator (tPA) for three days. This treatment resulted in the disappearance of the thrombus and the tricuspid insufficiency. No adverse effects were noted. Treatment with tPA should be considered in intracardiac thrombus formation with rapidly progressive heart failure in the neonate.

As central catheters are used extensively in neonates for parenteral nutrition or administration of medication, formation of both infected and non-infected thrombi on the endocardium is increasingly observed. Especially in neonates with very low birth weight such thrombus formation may lead to life threatening situations. Treatment of these cases is difficult.[1–3]

We report on our experience with tissue type plasminogen activator (tPA), a new thrombolytic agent, in a newborn with rapidly progressive heart failure due to thrombus formation on the tricuspid valve.

Case report
The patient was a girl with intrauterine growth retardation who was born by caesarean section because of fetal distress. Gestational age was 32 weeks, birth weight 900 g, and height 35 cm. Apgar scores were 8 and 8 at 1 and 5 minutes respectively. On the second day a central venous line was introduced via the right brachial vein for parenteral nutrition. On chest radiography, the tip of the catheter was located at the entrance of the right atrium. No umbilical catheters were used. There were no problems until the 10th day when lethargy, mottling of the skin, increasingly frequent episodes of apnoea and bradycardia, and increasing oxygen demand developed.

The suspected diagnosis of septicaemia was confirmed later by growth of coagulase negative staphylococcus in three bottles from two separate peripheral blood cultures. These staphylococci all had the same susceptibility profile to antibiotics. Treatment with cefotaxime, amikacin, and vancomycin and supportive medication was started.

On the 12th day of life the clinical situation again deteriorated with impaired peripheral circulation, tachycardia, tachypnoea, generalised oedema, and hepatosplenomegaly. Auscultation revealed a gallop rhythm, an additional click that could be differentiated from the third heart sound, and a holosystolic grade III murmur that had been absent previously and was situated parasternally in the left fourth intercostal space. Acute heart failure was diagnosed. Echocardiography showed no congenital heart disease but a vegetation on the atrial side of the septal leaflet of the tricuspid valve, measuring 2×3 mm (fig 1). The right atrium was dilated. Echo Doppler revealed moderate tricuspid valve insufficiency with the jet lining the free margin of the vegetation.

Laboratory investigations showed microscopic haematuria, thrombocytopenia with a platelet count of 28×10^9/l, white cell count of 5×10^9/l with 39% polymorphonuclear neutrophils, haemoglobin concentration of 104 g/l, and a packed cell volume of 0·35. C reactive protein was increased to 92 mg/l (normal value is <5 mg/l). There was a slight metabolic acidosis but no other electrolyte disturbances.

Because of the acutely deteriorating clinical condition it was decided to attempt lysis of the vegetation. Tissue type plasminogen activator (tPA, Actilyse, Boehringer Ingelheim) was administered through the central venous line in a dose of 0·5 mg/kg during 10 minutes followed by a continuous infusion of 0·2 mg/kg/hour. The antibiotic treatment was continued. The patient's general condition rapidly improved and tachycardia and generalised oedema disappeared. One day after the start of the treatment with tPA, the holosystolic murmur disappeared, two dimensional echocardiography showed a diminution of the vegetation on the tricuspid valve, and echo Doppler showed a decrease of the tricuspid valve insufficiency. However, an echodense mass seen on the septum in the right ventricle, probably a

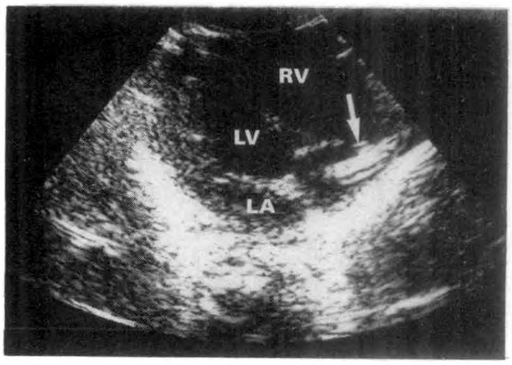

Figure 1 Ultrasound four chamber view of the heart showing the vegetation (arrow) on the tricuspid valve. LV=left ventricle, RV=right ventricle, LA=left atrium.

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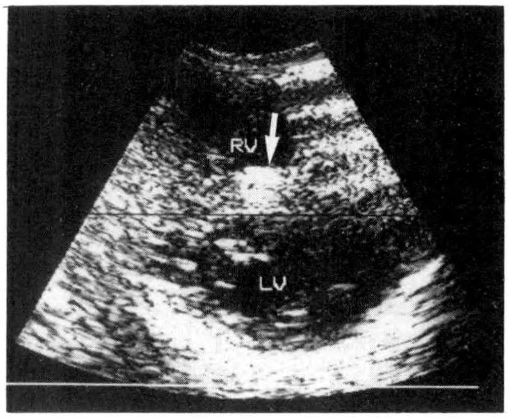

Figure 2 Ultrasound parasternal view of the heart showing the mass (arrow) in the right ventricle on the septum. LV=left ventricle, RV=right ventricle.

detached and entrapped part of the original vegetation (fig 2). On the third day of treatment with tPA, this thrombus had disappeared; the original vegetation was hardly visible. One day later no thrombi could be demonstrated and the tricuspid regurgitation had disappeared completely. Infusion of tPA was then stopped. During this treatment no bleeding tendency at puncture sites was observed, there were no respiratory disturbances, no ecchymoses or purpura appeared, and transfontanellar echography showed no intraventricular haemorrhages. Activated partial thromboplastin time, prothrombin time, and plasma fibrinogen concentration remained normal. Hepatosplenomegaly disappeared during the days after cessation of treatment. The central venous catheter was removed on the 37th day of life: bacterial culture of the tip remained negative. Antibiotic treatment was continued for a total of six weeks. Echocardiography after three weeks and three months was normal; electrocardiography and transfontanellar echography always remained normal.

Discussion

Since central catheters have been used in neonates septicaemia, mainly by coagulase negative staphylococcus, and thrombus formation are increasingly seen as complications.[1–3] When thrombi develop on the endocardium they may lead to life threatening situations such as dissemination of emboli in the lungs or the systemic circulation, obstruction of the valves, or valvular insufficiency. The latter may result in serious functional disturbances and heart failure. Endocardial vegetations of more than 1–2 mm can be diagnosed by two dimensional sector echocardiography, the accompanying functional disturbances such as valvular regurgitation by combined Doppler investigation. The treatment of thrombus formation with haemodynamic implications remains a difficult decision. The most radical treatment consists of the surgical removal of the thrombus: such treatment is, however, not without risks when the patient's condition is precarious.[4–6] An alternative which has only exceptionally been tried in infants is lysis of the thrombus by pharmacologic agents.[7]

In our patient there were sufficient indications for septicaemia by coagulase negative staphylococcus and this was treated with antibiotics and supportive measures. Intracardiac thrombus formation was suspected when the general condition again deteriorated, a heart murmur appeared, and heart failure developed. The diagnosis was confirmed and its functional implications established by echography. Surgical removal of the thrombus was not considered for three main reasons: presence of a severe infection, haemodynamic instability, and small body size. We instead decided to use thrombolytic treatment, being well aware of the risks such treatment could engender in this critically ill patient. The main problem was the possibility of dissemination of a probably infected thrombus. We could, however, expect that the thrombolytic agent would also dissolve the disseminated thrombi.

We opted for tPA, which is a recently introduced specific thrombolytic agent obtained by DNA recombination and which is identical with the endogenous human glycoprotein.[8] Compared with the first generation thrombolytic agents urokinase and streptokinase, tPA has several theoretical advantages.[9] First, it exerts its action on fibrin locally without activating the plasminogen in the circulation and therefore without causing generalised thrombolysis. Furthermore, because of its identity with the human endogenous glycoprotein, it has no immunising capacity and has identical biochemical and kinetic properties. Finally, it has a short half life time of approximately five minutes, allowing an easier monitoring of the treatment. In our patient the treatment resulted in the diminution of the vegetation on the tricuspid valve and a decrease of the tricuspid insufficiency with improvement of the haemodynamic situation after one day. After three days no thrombi could be demonstrated and the thrombolytic treatment could be interrupted. No complications, more specifically no bleeding tendency or further dissemination of the thrombus, were observed. These results were confirmed during a follow up of three months.

tPA has been used extensively in adults but in children and certainly in neonates the experience is very limited. It has been used, apparently with success, in the treatment of aortic thrombosis in a 4 day old premature infant[10] and of a pulmonary embolism in a 19 month old boy.[11] Recently, successful treatment with tPA of various thromboembolic conditions in children from different age groups was described and dosage schemes were proposed.[12] If our experience is confirmed intracardiac thrombus formation with rapidly progressive cardiac failure should be added to the list of indications for tPA treatment.

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Respiratory timing in intubated neonates with respiratory distress syndrome

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Abstract

Respiratory timing was studied in 100 babies ventilated for respiratory distress syndrome (RDS) during a brief period of continuous positive airway pressure. For the 76 spontaneously breathing babies the mean (SD) inspiratory and expiratory times were 0·31 (0·06) and 0·41 (0·12) seconds. Respiratory rate was predominantly modulated by expiratory time. The severity of RDS was the main influence on expiratory time.

There have been a number of studies of respiratory rate in well neonates, both term and preterm.[1–3] Little is known, however, about respiratory rate in preterm babies with respiratory disease.

A baby's respiratory rate is determined by the duration of each breath, which, in turn, is fixed by the time spent in inspiration (Tin) and expiration (Tex). How changes in respiratory rate are modulated by changes in Tin and Tex, in sick babies with respiratory disease, is not known. Hird and Greenough measured inspiratory time in intubated babies with respiratory distress syndrome (RDS) during disconnection from the ventilator, but the expiratory time was not measured.[4]

The aim of this study was to examine the relationships between respiratory rate and Tin and Tex, in a group of intubated babies with RDS.

Patients and methods

Over a nine month period, 100 intubated and ventilated babies with a clinical and radiological diagnosis of RDS were selected at random within six to 24 hours of birth. Babies were not enrolled in the study if they had been treated with sedative or paralysing drugs.

The respiratory pattern was studied at the time of enrolment, and classified as either 'apnoeic' or 'breathing'. If the baby was breathing, measurements were made of respiratory rate, Tin, and Tex. 'Breathing' babies were studied again at 2 and 7 days of age, provided that they were still being ventilated, were not apnoeic, nor receiving sedative or paralysing drugs at the time.

A pneumotachograph (Mercury F2L, dead space 1·7 ml, resistance 0·04 mm H_2O/l/second) was inserted between the endotracheal tube and the ventilator circuit. The flow signal obtained was recorded on paper at a speed of 25 mm/second. Measurements of Tin and Tex were made from the flow trace between points of zero air flow. The respiratory rate was calculated from these measurements. This pneumotachograph system has been demonstrated not to affect respiratory rate, or arterial blood gas tensions, when used for periods of up to 30 minutes in ventilated preterm babies.[5]

The babies were studied in the supine position, when quiet and making no gross body movements. No other assessment of arousal state was made. Arterial blood was analysed at the time of the study.

The mechanical ventilator was switched from the ventilating mode to provide 5 cm H_2O continuous positive airway pressure (CPAP) only. The inspiratory and expiratory flow pattern was observed for 30 seconds. Babies who made no breathing efforts in this period were classified as apnoeic, and mechanical ventilation was resumed. Babies who were breathing then had a further 30 second recording of the flow trace before ventilation was resumed. The flow traces from each breathing baby were examined, and a sequence of five consecutive regular breaths was selected for timing analysis. The mean measurement in these five breaths were taken as respiratory rate, Tin, and Tex.

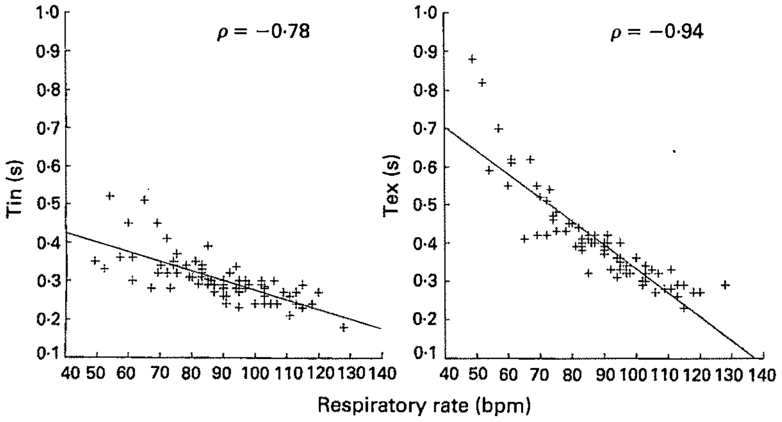
Results were expressed as mean (SD). The effects of other factors on respiratory timing were explored using stepwise multiple regression analysis. The relationships between timing variables were examined using Spearman's rank correlation coefficient. The relationships between respiratory rate and Tin and Tex were examined across the group on day 1, and in individual babies who had been followed sequentially. The slopes of the regression lines for rate versus Tin, and rate versus Tex, were calculated for each baby that had been followed in this way, and the means of these slopes were taken.

The study was approved by the hospital human ethics committee.

Results

The data recorded from 100 babies enrolled on the first day of life shown as mean (SD), were: gestation 28·7 (2·8) weeks and birth weight 1259 (571) g; there were 58 boys and 42 girls. Hydrogen ion concentration was 48·1 (10) nmol/l, carbon dioxide tension ($P\text{CO}_2$) 5·6 (1·6) kPa, oxygen tension ($P\text{O}_2$) 9·3 (3·4) kPa, and alveolar–arterial oxygen gradient ($A-aD\text{O}_2$) 4·6 (2·7) kPa.

Of the 100 babies, 76 were classified as breathing, and 24 as apnoeic, when studied on the first day. Of the 76 breathing babies, 26 were also studied on day two, and of these, 11 were studied again on day seven.



Relationship of Tin and Tex to respiratory rate in 76 babies studied on first day of life. Spearman's rank correlation coefficient (ρ) is shown for each relationship.

There were no significant differences in sex ratio, hydrogen ion concentration, Pco_2, Po_2, or $\text{A}-\text{aDo}_2$ between the apnoeic and breathing groups. The apnoeic babies were less mature than the breathing babies (26·6 (2·3) *v* 29·1 (2·8) weeks' gestation, $p<0·05$).

Timing analysis from the 76 records on day 1 gave the following results: respiratory rate 88·5 (17·8), range 48–138, breaths/minute (bpm); Tin 0·31 (0·06) seconds; and Tex 0·41 (0·12) seconds. Coefficient of variation for the five breaths analysed was 9·2% for Tin and 8·7% for Tex. The figure shows the relationships between respiratory rate and Tin and Tex for all 76 babies studied on day 1. The slopes of the regression lines were: −2·5 ms/breath for Tin and −6·2 ms/breath for Tex. The mean slopes of the regression lines for those babies followed sequentially were: −2·8 ms/breath for Tin and −13 ms/breath for Tex.

Stepwise multiple linear regression showed no statistically significant effect on day 1 respiratory rate, Tin, or Tex for the variables: gestation, birth weight, hydrogen ion concentration, Pco_2, or Po_2. $\text{A}-\text{aDo}_2$ was significantly related to respiratory rate ($r=0·43$, $p<0·001$), Tin ($r=-0·03$, $p<0·05$), and Tex ($r=-0·41$, $p<0·001$). Thus the higher $\text{A}-\text{aDo}_2$, the faster the respiratory rate and the shorter Tin and Tex.

Discussion

Of 100 unsedated ventilated babies with RDS, 76% were found to be breathing, and 24% apnoeic, during a brief period when ventilation was stopped in the period 6 to 24 hours of age. There were no differences in hydrogen ion concentration, Pco_2, or Po_2 which might have caused this. The apnoeic babies were significantly less mature than those who were breathing. Other clinical factors which could have influenced the babies' tendency to breathe (for example, sepsis or intraventricular haemorrhage) were not recorded.

The mean respiratory rate found in this study was fast (88·5 bpm), with a short Tin (0·31 s) and Tex (0·41 s). Bourtourline-Young and Smith found a mean respiratory rate of 33 bpm in well preterm babies.[2] Seguin *et al*, in a study of six preterm babies with RDS (who were not intubated and ventilated) found a mean respiratory rate of 73 bpm, with Tin of 0·35 seconds, and Tex of 0·48 seconds.[3] Hird and Greenough found the median Tin of intubated preterm babies with RDS to be 0·275 seconds when disconnected from the ventilator and 0·35 when on endotracheal CPAP.[4] They did not study expiratory time.

Maintenance of adequate lung volume in preterm babies with lung disease is dependent on dynamic mechanisms. Such mechanisms include continued contraction of inspiratory muscles, and partial glottic closure, during expiration. Glottic closure produces the familiar grunting respirations, and retards expiratory gas flow.[6] Once intubated, a baby is deprived of this mechanism for preserving lung volume. Rapid respirations with short expiratory times may lead to gas trapping which may in turn help to preserve an adequate functional residual capacity. The mean Tex of 0·41 seconds found in this study may indicate that some babies had expiratory times of less than the three respiratory time constants said to be necessary for complete expiration

Respiratory rate was found to be modulated predominantly by changes in Tex, with Tin playing a lesser part. This was found in the breathing babies as a group on day 1, and in individual babies followed up over a period of time. Irritant receptors in the bronchial tree are stimulated by atelectasis, and this, via a vagally mediated reflex, is probably what leads to shortening of Tex, which, in turn, will raise end expiratory lung volume and reverse atelectasis.[7]

Interestingly, Pco_2, Po_2, arterial hydrogen ion concentration, and gestation had no significant independent effects on respiratory timing. The influence of arterial blood gas tensions was studied in the group as a whole. The effects were not studied in individual babies. The only factor studied which did influence timing was $\text{A}-\text{aDo}_2$, which is a measure of oxygen diffusion ability. Thus the more severe the lung disease, the faster the respiratory rate, and the shorter Tin and Tex, with Tex again being affected more than Tin. How $\text{A}-\text{aDo}_2$ influences respiratory timing without affecting Po_2 is not clear. It is likely that abnormal $\text{A}-\text{aDo}_2$ measurements were associated with other abnormalities of lung function (for example, compliance) that were not measured in this study.

In conclusion, intubated babies with RDS tend to breathe quickly, with short inspiratory and expiratory times. Respiratory rate is predominantly modulated by changes in expiratory duration and this, in turn, is influenced by the severity of the lung disease. An understanding of why, and how, preterm babies with RDS become tachypnoeic should help in their management.

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Intraventricular haemorrhage after aspiration of ventricular reservoirs

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Abstract

A previously unrecognised complication of aspirating ventricular reservoirs is described. Four infants developed fresh bleeding into the cerebrospinal fluid after reservoir taps; ultrasound confirmed intraventricular blood clot in one case. The technique for aspirating the reservoir may have an important bearing on the incidence of this complication.

The use of ventricular reservoirs in the management of the newborn infant with posthaemorrhagic hydrocephalus was first described in 1980.[1] It has since been shown to be an effective method for 'buying time'. It allows time to stabilise the infant, prevents multiple lumbar punctures and ventricular taps, allows more aggressive management of raised intracranial pressure, and enables clearance from the cerebrospinal fluid (CSF) of blood and protein before insertion of a ventriculoperitoneal shunt. In addition, the incidence of shunt infection is significantly reduced when reservoirs are used initially with later shunting as compared with early primary insertion of a shunt.[2] We review our experience of 10 cases who had reservoirs inserted over a three year period and describe a previously unrecognised complication—late intraventricular haemorrhage.

Patients and methods

Between January 1988 and December 1990, 10 infants had reservoirs inserted at the Leeds General Infirmary for posthaemorrhagic hydrocephalus. Eight of the infants were ventilated for hyaline membrane disease and all suffered at least a grade II intraventricular haemorrhage in the first week of life. This was followed by progressive ventricular dilatation. Indications for inserting a reservoir were an occipitofrontal head circumference which was larger than the 97th centile, difficulty with lumbar punctures and/or symptoms of raised intracranial pressure. The reservoir was inserted in the parieto-occipital region with the tip lying in the occipital horns of the lateral ventricles and the dome lying subcutaneously.

Details of CSF removal

	Gaskill et al[3]	*Leonhardt et al*[4]	*Leeds General Infirmary*
Median (range) volume removed (ml) at each tap	* (5–15)	6 (1–15)	11 (1–36)
Median (range) tap frequency/day	2 (up to 3)	2 (1–4)	1 (0·5–3)
Needle gauge used	27	25–27	23

*Median not stated.

Subsequently, the reservoir was tapped sufficiently often to control excessive head growth or symptoms of raised intracranial pressure (most commonly apnoea and or bradycardia). The CSF was removed through a 23 gauge butterfly needle usually by free drainage. Occasionally gentle suction was applied by a syringe when CSF flow was sluggish. All patients had regular cranial ultrasound examinations and the CSF sent for microscopy and culture. Shunt insertion was performed when the CSF became clear of red blood cells and the protein concentration was less than 2 g/l.

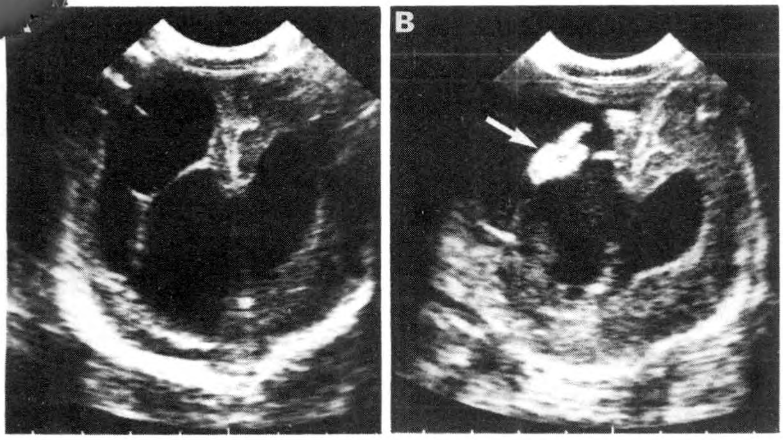
Results

The median (range) weight of the infants treated with a reservoir was 1100 g (675–3560 g). The gestation ranged from 23 to 41 weeks. The reservoirs were inserted at 6 to 68 days postnatal age (median 27 days).

There were no reservoir infections. Two infants became hyponatraemic, probably due to CSF removal as their serum sodium was normal before this removal; this was corrected with sodium supplements in the feeds. No infant became hypoalbuminaemic. One reservoir became blocked and required revision: no specific cause was identified but infection was excluded.

There were four cases of late intraventricular haemorrhage after reservoir insertion. These episodes occurred at 13, 17, 24, and 33 days after insertion. The CSF had become clear just before these bleeds. Fresh blood suddenly appeared in the CSF and red cell counts rose to between 10^3/l and 10^5/l. In one case a new blood clot was seen on cranial ultrasound scan at the time of the haemorrhage. This bleed occurred into a porencephalic cyst on the opposite side to the reservoir (fig). Clotting studies at the time of the haemorrhage were normal.

The method and amount of cerebrospinal fluid removed is compared in the table with



Coronal ultrasound scans showing (A) large right sided porencephalic cyst and dilated ventricles before the haemorrhage and (B) echodensity (arrowed) associated with haemorrhage in the region of the porencephalic cyst.

previous series of Gaskill *et al*[3] and Leonhard *et al.*[4] In those who had a late haemorrhage, the method of removing the CSF was analysed in more detail. There was no significant change in the volume and frequency of taps just before the haemorrhage. Those who had a haemorrhage had a similar volume and frequency of taps as those who did not. In the one case where an ultrasound scan confirmed the bleed, suction was used to remove CSF just before the bleed.

There were no symptoms in any of the patients at the time of the haemorrhage, but there was a delay in insertion of the ventriculoperitoneal shunt in those who suffered a haemorrhage (median age of insertion 80 days) compared with those who did not (median 20 days).

Discussion

Late haemorrhage as a complication during reservoir management of posthaemorrhagic hydrocephalus has not previously been reported. Although not associated with any symptoms, the four affected patients had a delay in conversion of the reservoirs to ventriculoperitoneal shunts. The possibility of such a complication was highlighted in a commentry by Bannister on the paper by Leonhardt *et al.*[4] She emphasised that the removal of CSF via a reservoir is not physiological because it does not allow a smooth transition of intracranial pressure. Significant pressure differentials may be produced in the brain leading to rupture of friable blood vessels. The method of removing the CSF will have an important influence on the magnitude of these pressure differentials.

In comparison with Leonhardt *et al* and Gaskill *et al* (table), we removed on average more CSF less frequently with a larger gauge needle and, on occasion, with the application of gentle suction. These factors may be important and possibly explain our observation of secondary intraventricular haemorrhage. In order to minimise the pressure shifts within the brain, we recommend more frequent taps (at least daily), removing smaller volumes (<10 ml) and using smaller gauge needles (25 G, 27 G). The CSF should be allowed to drip out and not aspirated at any stage, no matter how slow the drainage. Alternative methods of CSF removal include temporary or continuous drainage. The latter entails a high risk of secondary infection and makes nursing of the infant difficult. Temporary drainage may offer a more physiological alternative to tapping without increasing the risk of infection.

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PERINATAL BIOLOGY

Prenatal treatment with thyrotrophin releasing hormone to prevent neonatal respiratory distress

Francis de Zegher, Bernard Spitz, Hugo Devlieger

Three major strategies, that are not mutually exclusive, are being developed to tackle the problem of respiratory distress syndrome in preterm infants. The first is to prevent premature birth itself through improved obstetrical follow up and care; however, this has proved not to be an easy task.[1] The second is to optimise the postnatal treatment of infants with respiratory distress through the availability of neonatal intensive care units and their motorised or airborne transportation teams, as well as through the use of novel medication and techniques, for example, the endotracheal administration of biosynthetic pulmonary surfactant, artificial ventilation with liquid or high frequency oscillation, and extracorporeal membrane oxygenation. The third strategy is to administer, in cases of threatening premature birth, a treatment to the fetus that accelerates the fetal preparation for neonatal respiration, thus preventing the development of neonatal respiratory distress.

The concept of accelerating fetal maturation was launched in 1969, when Liggins noted as an epiphenomenon of his study on the initiation of parturition in the ewe that the infusion of dexamethasone had a stimulatory effect on the lung aeration of prematurely delivered lambs.[2] This pioneering observation has now been repeatedly confirmed and has been extended to numerous mammalian species, including the human. In addition, the underlying pathophysiological mechanisms are increasingly well understood.[3] The principle has been applied successfully in human perinatal medicine, where the administration of glucocorticoids to the pregnant woman—and thus transplacentally to the fetus—has served as the 'gold standard' of fetal maturational treatment for nearly two decades.[4 5]

The regulation of lung development during fetal life has been documented extensively to be under multihormonal control.[3] Thyroid hormones in particular appear to stimulate fetal pulmonary maturation. However, as thyroid hormones and thyroid stimulating hormone (TSH or thyrotrophin) fail to cross the human placental barrier sufficiently,[6] thyrotrophin releasing hormone (TRH) has become the prime focus of attention.[7] There is evidence suggesting that TRH may also be useful in accelerating fetal maturation through its nonendocrine actions.

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Thyrotrophin releasing hormone

In the search for hypothalamic hypophysiotropic peptides, a tripeptide stimulating the release of thyrotrophin by the mammalian anterior pituitary was the first hypothalamic releasing hormone to be structurally identified; this tripeptide, discovered in 1969, pyroglutamyl-histidyl-proline amide, was designated TRH.[8 9]

TRH is the smallest of the known peptide hormones and appears to have ancient origins pre-existing its hypophysiotropic properties, as evidenced by the presence of TRH in the brain and neural ganglia of some invertebrate species lacking a pituitary gland.[10]

The neuronal biosynthesis of TRH follows classical peptide synthesis pathways. The first post-transcriptional peptide, pre-pro-TRH, contains five repeating sequences coding for the tetrapeptide Gln-His-Pro-Gly with at least two flanking region peptides. Before entering axonal processes, pre-pro-TRH is cleaved into the tetrapeptide (pro-TRH). Finally, Gly is exchanged for a terminal amide, and TRH (packaged in storage granules) is ready for secretion.[11]

TRH has been localised in numerous regions of the mammalian nervous system.[11 12] The classical TSH-regulating hypophysiotropic neurons originate from the paraventricular nucleus and project to the median eminence of the hypothalamus.[11] TRH has been detected in the human fetal hypothalamus as early as 10–12 weeks' gestation and concentrations are thought to increase progressively towards term.[13] TRH is present in the extrahypothalamic brain of the human fetus; it has been detected in the cerebellum as early as the ninth week of gestation.[14] TRH has also been found in the nucleus tractus solitarius, which participates in the control of breathing; in vitro evidence strongly supports a role for TRH in the physiological regulation of rhythmic breathing in mammals.[15] Other TRH-containing neurons include those localised in structures of the limbic system (effect on arousal), in a descending neural pathway from brain stem raphe nuclei projecting to spinal motor neurons (effect on muscle function) and those forming the intermediolateral column (cardiovascular effects). The mammalian placenta,[16] retina,[17] and male reproductive organs[18] have also been reported to contain TRH. However, the most abundant presence of TRH in the developing mammal is found in the gastrointestinal system, particularly in the islets of the pancreas.[17 19–22]

TRH is subject to rapid enzymatic breakdown in tissues (including the anterior pituitary), serum and other body fluids, yielding several metabolites of uncertain physiological significance.[10] In the human adult, the pharmacokinetics of TRH are partly regulated by the thyroid status; in euthyroid conditions, the plasma half life of TRH is almost seven minutes.[23] In pregnant women, the serum TRH degrading activity is lower than in euthyroid, non-pregnant adults.[24] Intravenously infused TRH appears to be distributed exclusively in the extracellular fluid.[23] The permeability of the blood-brain barrier to TRH is poor.[25] TRH, in contrast to thyroxine and TSH, crosses the human placenta readily.[6 26] The pharmacokinetics of TRH in the human fetus and newborn have not yet been reported. Raised plasma TRH concentrations, largely from extrahypothalamic origin, have been documented in the fetal rat and sheep at midgestation.[19 20] The cord serum TRH concentration of the human infant at term birth is raised and falls within the days after birth.[20] The TRH degrading activities in human fetal serum and in human neonatal cerebrospinal fluid are very low compared with adult standards.[24 27]

The TRH receptors localised in the pituitary, in the gastrointestinal tract, and in the nervous system resemble each other.[28 29] Although the latter are ubiquitously distributed, the highest densities are found in limbic structures, particularly the hypothalamus and the amygdala, in the brain stem, the cerebellum, and the grey matter of the spinal cord; lower densities are present in the dorsal roots and ganglia of the spinal cord.[30] The TRH receptor has now been cloned and identified as a novel member of the family of transmembrane, G protein coupled receptors. The expression of the TRH receptor is regulated in part by cell specific post-transcriptional mechanisms (mRNA stability) (M C Gershengorn. Presented at Endocrine Society Meeting, Washington, 1991). TRH can down regulate its own receptor through time and dose dependent mechanisms, resulting in cellular desensitisation to TRH (J Perlman, M C Gershengorn. Presented at Endocrine Society Meeting, Washington, 1991).[30] Whereas pituitary recovery from TRH desensitisation occurs presumably within hours, animal studies indicate that complete neuronal recovery may be delayed for one week.[31 32] TRH binding to its receptor on the cell membrane stimulates a second messenger system, probably inositol triphosphate/diacylglycerol, which acts to increase intracellular free calcium by mobilisation from intracellular pools and by increasing transport via cell membrane calcium channels.[33] In the thyrotrophs of the anterior pituitary, TRH stimulates secretion and glycosylation of TSH, but does not increase the production of mRNA for either the α or the β subunit of TSH.[34]

There is virtually no direct evidence available regarding the maturation of human fetal TRH receptors. However, TRH has long been known to stimulate TSH secretion in the premature infant born at 20 weeks' gestation, indicating the presence of pituitary TRH receptors by this age.[35] Subsequent studies revealed that the intravenous injection of TRH to the pregnant woman within three hours of delivery increases the cord blood concentration of TSH at term and preterm birth.[26 36 37] The human fetal TSH reponse to maternal administration of TRH was recently evaluated in utero between 25 and 37 weeks' gestation; this study demonstrated a striking fetal TSH response of up to 100 mU/l within 10–30 minutes from the intravenous TRH injection.[38] It is noteworthy that the TSH response of the third trimester human fetus to exogenous TRH is at least in the range of the TSH surge normally observed within the first hours after birth and presumably elicited by endogenous TRH of hypothalamic origin.[39 40] In the human, maternal intravenous administration of TRH does not appear to influence fetal prolactin secretion.[37]

The fetal thyroid gland becomes increasingly responsive to endogenous TSH stimulation throughout the third trimester of pregnancy, as evidenced by gradually rising serum thyroxine concentrations in the face of relatively constant serum TSH concentrations.[41 42] Therefore, the TRH evoked TSH response is considered to be the principal mediator of the changes in fetal thyroid status that occur after exposure to exogenous TRH. In the term human fetus, these changes include a significant rise in serum thyroxine concentrations within 60 minutes,[26 37] as well as a doubling of the circulating tri-iodothyronine concentrations within 120 minutes from intravenous maternal TRH injection.[36] The increase of serum thyroxine is exclusively of fetal thyroidal origin, whereas the augmented concentrations of bioactive tri-iodothyronine are largely derived from thyroxine deiodination in fetal peripheral tissues.[20] This deiodination activity has been correlated with the fetal serum concentration of endogenous cortisol and can be further stimulated by exogenous glucocorticoids.[20 43] The TRH induced serum concentrations of thyroxine and tri-iodothyronine return to baseline concentrations within a few hours.[26 31 36]

Thyrotrophin releasing hormone and fetal preparation for neonatal respiration

Normal neonatal respiratory function requires sufficient and orchestrated maturation of multiple fetal organs and systems. Exogenous TRH may influence fetal maturation either directly or indirectly, through its effect on the fetal thyroid axis. Here, we provide a synopsis of the documented actions of TRH and thyroid hormones on the different fetal factors known to be involved in the preparation for neonatal respiration.

(1) PULMONARY SURFACTANT

Pulmonary surfactant is a surface active material synthesised and secreted by the type II epithelial cells of the alveoli of mammalian lungs. It consists of various lipids and proteins, forming a phospholipid monolayer that stabilises the alveoli at low lung volumes, thus preventing collapse and allowing for normal respiration. Insufficient alveolar presence of surfactant in the newborn leads to the clinical picture of hyaline membrane disease, the most frequent cause of neonatal respiratory failure and the leading cause of morbidity and mortality in prematurely born infants.[44]

It has been conclusively demonstrated that tri-iodothyronine accelerates the synthesis of surfactant in the fetal lung, particularly the synthesis of the phosphatidylcholine fraction. Moreover, tri-iodothyronine has a potent additive effect on the capacity of glucocorticoids to enhance surfactant synthesis. The actions of both hormones on the type II alveolar cells are mediated by different receptors and proceed through different biochemical mechanisms (reviewed by Ballard[44]).

(2) PULMONARY FLUID AND ION TRANSPORT

The fetal lung is filled with a chloride rich fluid that is actively secreted by the pulmonary epithelium towards the pharynx, where it is either swallowed or propulsed outside the oral cavity, thus contributing to the amniotic fluid (reviewed by Strang[45]). The intrapulmonary pressure exerted by lung fluid and modulated by the laryngeal sphincter seems to be an important stimulator of fetal lung growth.[46 47]

Normally, fluid production is diminished and reabsorption augmented in the immediate perinatal period. This is the result of the combined decreases in alveolar tension and in lymphatic and capillary hydrostatic pressure, of the increases in transpulmonary pressure and in plasma colloid pressure, and—most importantly—of the activated sodium transport by alveolar epithelial cells. These forces promote movement of sodium ions and water from the alveolar space through the apical membrane of epithelial cells into the lung interstitium, and finally into the lymphatic and systemic circulation. Insufficient or delayed clearance of lung fluid at birth leads to the clinical picture of 'transient neonatal tachypnoea', the most frequent cause of respiratory distress in infants born at term. Current evidence indicates that the principal mediators of the perinatal shift in lung fluid and ion transport are the catecholamines, atrial natriuretic peptide, and possibly vasopressin. Thyroid hormones and glucocorticoids appear to play a pivotal part as their increasing serum concentrations during development are required to sensitise the fluid flux to catecholamines.[48] Atrial natriuretic peptide has been shown to decrease fetal lung fluid production possibly through endocrine and pulmonary paracrine pathways.[49 50] The demonstration that tri-iodothyronine and glucocorticoids increase the synthesis of atrial natriuretic factor by the alveolar type II cells suggests a stimulating effect of both hormones on this aspect of fetal lung maturation.[50]

(3) THE CARDIOVASCULAR SYSTEM

At birth, the respiratory organ of the fetus, the placenta, is replaced by the lungs as the site of gas exchange. Moreover, metabolic and thermoregulatory activities increase, leading to a substantial rise in oxygen consumption. These respiratory adaptations are largely mediated by circulatory changes.

The switch in respiratory organ involves the constriction of the ductus arteriosus and a dramatic fall in pulmonary vascular resistance. Both these phenomena appear to be essentially the result of shifts in arachidonic acid metabolism involving lipoxygenase products (leukotrienes) and cyclo-oxygenase products (prostaglandins and thromboxane).[51] Thyroid hormones facilitate the postnatal closure of the ductus arteriosus, as suggested by the raised incidence of patent ductus arteriosus in infants with congenital hypothyroidism.[52] Glucocorticoids are also known to have a maturational effect on the ductus arteriosus, by decreasing the ductus' sensitivity to the relaxing action of prostaglandin E_2.[53]

The fulfilment of the neonatal rise in oxygen demand is partly accomplished through a marked increase in cardiac output, which is in turn mainly mediated by augmented concentrations of circulating catecholamines acting on myocardial β adrenergic receptors. To obtain the necessary β adrenergic receptor availability, the presence of thyroid hormones appears to be crucial.[54] Interestingly, the prenatal circulating thyroid hormone concentrations are more important than the postnatal concentrations for this vital adaptive function.[55] A recent cardiotocographic study of the preterm human fetus has shown that the maternal administration of TRH increases within an hour the frequency of fetal heart rate accelerations and increases the fetal heart rate variability; increases in these two variables are currently considered as indicators of improved fetal well being (W Gyselaers *et al*, unpublished observations).

(4) FETAL BREATHING, PULMONARY GROWTH, AND RESPIRATORY MUSCLES

Intermittently, the fetus makes rapid and irregular breathing movements that are of a magnitude comparable with postnatal respiration. These breathing movements participate in the circulation of lung fluid within the respiratory tract and provoke periodic oscillations in the pulmonary transmural pressure, both of which contribute to normal growth of the fetal lungs.[56]

The breathing activity in utero is also important for adequate development of the diaphragm and the intercostal muscles.[56] The fetal efforts of these respiratory muscles have a profound effect on the configuration of the neonatal chest wall and the condition of these muscles at birth largely determines the infant's potential for efficient ventilation, particularly when the infant is born prematurely.[57]

In the fetal lamb, the intravenous or intracerebroventricular administration of TRH elicits—apparently through non-endocrine pathways—a behavioural arousal with increased body and eye movements and provokes a marked stimulation of fetal breathing movements, which become continuous, faster, and deeper.[58 59] These data have even led to the suggestion that the presumed surge in TRH secretion at birth plays a part in the switch from a fetal to a postnatal breathing pattern.[58]

The effect of TRH on breathing activity in the human fetus has not been reported. However, the cardiotocographic study of the human fetus after administration of TRH to the pregnant woman provides indirect evidence for an effect of TRH on human fetal behaviour and breathing comparable with the effect observed in the fetal lamb (W Gyselaers *et al*, unpublished observations). Indeed, the reported increase in the frequency of fetal heart rate accelerations suggests an increase in fetal body movements, as 91–98% of fetal heart rate accelerations are normally associated with fetal body movements.[60] [61] Similarly, the reported increase in fetal heart rate variability is suggestive of an increase in fetal breathing movements, as there is also a close and positive correlation between these two variables.[60]

Conclusion and outlook

The available neuroendocrine and physiological information provides a solid basis for the clinical evaluation of prenatal TRH treatment in the prevention of neonatal respiratory distress. The effects of prenatal TRH treatment are expected to be beneficial, in part because of their striking synergism with the maturational actions of glucocorticoids.

The first analyses of the ongoing clinical trials suggest a maturational effect of prenatal TRH treatment on top of the known favourable actions of prenatal glucocorticoid treatment (G C Liggins, personal communication).[31] There are no reported studies examining the clinical effect of prenatal TRH treatment in the absence of concomitant glucocorticoid administration.

Further basic and clinical research is needed to establish firmly the combined treatment of glucocorticoids and TRH as the novel prenatal treatment of choice. This research will have to include studies examining the timing and dosage variables in the treatment schedules. In this way an optimal, dual treatment regimen could be developed.

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REGULAR REVIEW

On the horizon: neonatal lung transplantation

N Scott Adzick

There are several congenital lung lesions that result in severe pulmonary hypoplasia and neonatal death. These malformations include congenital diaphragmatic hernia (CDH), oligohydramnios induced pulmonary hypoplasia, and congenital cystic adenomatoid malformation of the lung. Severely affected newborns are not salvageable by current surgical techniques or medical treatment, although one new experimental approach is prenatal surgical intervention in highly selected cases.[1–3] In older children respiratory failure is the final common pathway in severe cases of bronchopulmonary dysplasia, cystic fibrosis, and primary pulmonary hypertension. One potential treatment for all of these fatal problems is lung transplantation.

Adult lung transplantation

Before 1980, all 40 attempts at single lung transplantation worldwide failed.[4] Over the past decade adult lung transplantation has been successfully implemented at more than 50 medical centres worldwide. After years of discouraging results success was obtained because of multiple factors including the availability of cyclosporin for immunosuppression and the use of the omentum to protect and revascularise the crucial bronchial anastomosis. The primary indications for lung transplantation in the adult age group are pulmonary fibrosis, emphysema, cystic fibrosis, and Eisenmenger's syndrome. Results have steadily improved with experience and the overall one year survival was 79% in a series of 66 patients reported by the pioneering group at Washington University in St Louis.[5] Single lung transplantation may partially supplant heart-lung transplantation as the lung is a 'spare' organ whose use does not preclude use of the heart and the contralateral lung for other patients. However, potential recipients with suppurative lung disease such as cystic fibrosis require either bilateral sequential lung transplants in which both infected lungs are replaced at one setting or an en-bloc heart-lung transplant. In the latter circumstance the recipient heart can then be donated to another patient—the 'domino' operation.[6]

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Paediatric lung transplantation

Although the experience with lung transplantation in adults has been very encouraging, the lung transplantation effort in children is just beginning. Thirty four paediatric lung transplants are recorded in the International Lung Transplant Registry at Washington University and the indications included severe bronchopulmonary dysplasia, cystic fibrosis, and refractory pulmonary hypertension. The youngest recipient was 16 months of age, and the overall actuarial one year survival was 60%. However, paediatric lung transplantation is hampered by the paucity of potential donors and a lack of understanding of many physiological responses to transplantation in immature recipients. Cadaveric or living related donation of a reduced size lung (pulmonary lobe or segment) may help solve the donor shortage problem for lung transplantation in infants and children. It is essential that experimental studies be crafted to address some of the biological questions.

Neonatal lung transplantation

For neonates with fatal pulmonary hypoplasia, biological tissue replacement is the only potentially satisfactory solution. The donor lung graft must be able to grow and adapt to increasing functional demand over the long potential lifespan of the young recipient. But the logistics of lung transplantation are particularly demanding for the neonatal recipient in whom rapid respiratory failure and short term extracorporeal membrane oxygenation (ECMO) support make the 'time window' for transplantation narrow. Because so few babies die in circumstances allowing organ donation, it is unlikely that an appropriate cadaver whole lung will be found during the limited time that the sick neonate is salvageable on ECMO.

Living related organ donation is a clinical reality in paediatric renal and liver transplantation,[7 8] and it represents the principal alternative for bone marrow transplant recipients.[9] This source of donor tissue has resulted in enhanced graft survival and diminished time on transplant waiting lists. Living related donation of a reduced size lung (either lobe or segment) may help solve the donor shortage problem for paediatric lung transplantaion. Donor pulmonary segmentectomy or lobectomy are straightforward surgical procedures. In contrast to cadaver donation, living related donation should be logistically simple, less costly, and readily available. In addition, it may result in enhanced graft survival due to potential immunological advantages. This concept has recently been tested clinically by the group at Stanford University. A 12 year old girl who was afflicted with end stage bronchopulmonary dysplasia had her right lung replaced with the upper lobe from her mother.[10] She is doing well one year after transplantation.

The principal candidate for neonatal lung transplantation is the baby with CDH with severe pulmonary hypoplasia. Recent studies have defined prognostic factors for babies with CDH diagnosed before birth.[11] Although ECMO has been a major advance in the treatment of respiratory insufficiency in neonates, some babies with CDH are still unsalvageable due to the severity of their pulmonary hypoplasia.[12] Using ECMO as a 'bridge' to lung transplantation in severely ill babies with diaphragmatic hernia would permit time to find a donor, perform the lung transplant, and surgically repair the diaphragmatic defect during the 10–14 day period when the baby can be maintained on the ECMO circuit. Transplantation of a reduced size lung (lobe or segment) for severe pulmonary hypoplasia offers a new approach for infants who are otherwise doomed.

There are several other congenital diseases that result in inadequate gas exchange at birth including oligohydramnios induced pulmonary hypoplasia, severe cases of congenital cystic adenomatoid malformation of the lung, and irreversible primary pulmonary hypertension. Recent clinical confirmation of the reduced size lung transplantation concept for neonates was provided by another case from Stanford University (KP Van Meurs *et al*, presented at the Children's Hospital National Medical Center ECMO Conference, 1991). A newborn with severe pulmonary hypertension could not be weaned from ECMO support. The left upper lobe and lingula from a 2 year old cadaveric donor were transplanted while the baby was on ECMO, with immediate weaning and decannulation. The baby initially did extremely well, but unfortunately died from an overwhelming rejection episode at age 8 months.

Before attempting lung replacement in neonates, it is necessary to clarify the anatomical, technical, physiological, and immunological problems in an animal model. To evaluate these considerations, our group developed a model of pulmonary lobar transplantation in neonatal pigs and studied pulmonary function and haemodynamics after transplanting the left lower lobe from a more mature (20–30 kg) donor to a neonatal (5 kg) recipient. The recipient's left atrial and pulmonary arterial pressures, cardiac output, pulmonary vascular resistance, and pulmonary static compliance were measured before and after left lower lobe transplantation.[13] In a separate series of experiments, the haemodynamic conditions of CDH were simulated by occlusion of the right (contralateral) pulmonary artery.[14] We found that lobar transplantation is technically feasible and physiologically sound. The static compliance of the lobar transplant is far greater than that of the native neonatal lung, and the transplanted lobe can accept the entire cardiac output during contralateral pulmonary arterial occlusion. Subsequent studies in a chronically immunosuppressed piglet model established the technique of an intercostal muscle flap to protect the bronchial anastomosis and used the gastrointestinal stapling device (US Surgical Corp) to 'sculpt' the apical segment of the left upper lobe from a 60 kg donor to fit into the neonatal recipient.[15] Other investigators have developed similar reduced size lung transplant techniques in beagle puppy and neonatal sheep animal models.[16] [17] The ability of an immature lung graft to grow in an immature recipient has been demonstrated in weanling pigs.[18]

A series of human adult and neonatal cadaver thoracic dissections were performed to determine the adult pulmonary lobe or segment with the proper size, orientation, and vascular and bronchial anatomy for use as a neonatal lung transplant.[15] The adult right middle lobe was found to be the best candidate for left lung replacement in the neonate with CDH. The adult right middle lobe, once removed, can be rotated 180° around its superior-inferior axis and the vessels and bronchus align well in the left chest of the neonate. The right middle lobe is the proper size to fill the neonatal left chest. If necessary, it can be sculpted with a stapling device to solve size disparity problems. The evaluation of the other adult lobes and segments revealed problems with vascular anatomy, vascular variability, size, or bronchial geometry which prevented consideration for neonatal lung replacement. It appears that the technical aspects of the lung transplantation operation will not be the limiting factor for success.

Consideration of lung transplantation in neonates and children provokes many unanswered questions. The growth potential of a denervated mature lobar graft in a neonatal environment is a major unresolved issue. What constitutes optimal immunosuppression in the neonate and how is it altered by growth and development? Likewise, the effects of chronic immunosuppression on the infant's growth and development is an unchartered area. Can chronic airway injury related to pulmonary rejection and infection be prevented? What is the best method to detect rejection in these patients as the transbronchial biopsy technique used in adults will probably not be applicable in babies? Finally, the recovery potential of the contralateral hypoplastic lung in babies with CDH after lung transplantation is an area worthy of investigation. Even if growth of the mature allograft does not occur, the transplant may function as a biological assist device until the remaining contralateral native lung tissue undergoes further alveolar growth. Thereafter, the allograft could be removed and the immunosuppression stopped. Recent encouraging clinical developments in neonatal transplantation, including cardiac transplantation for hypoplastic left heart syndrome[19] and successful transplantation of segmental liver grafts from living related adult donors into infant recipients with biliary atresia,[8] have made some of these questions more pressing. The outcome for tiny recipients of lung transplants will depend upon the answers to these questions.

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CURRENT TOPIC

Neonatal nurse practitioners—a view from perfidious Albion?

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Although the professional role of neonatal nurse practitioners (NNPs) has been fully integrated into many neonatal units outside the UK over the past decade,[1 2] there has to date been no such development in this country. Indeed, there have been serious reservations among members of the neonatal nursing profession concerning the introduction of NNPs given the current structure and funding of neonatal care in the UK.[3]

Despite these reservations, it has for several years been the view of most of the paediatricians and of many neonatal nurses within the Wessex region that the care of sick newborn infants could be improved by extending the role of the neonatal nurse. The case for extending the role has now been accepted by medical and nurse managers within the region and plans are well advanced to establish an educational course in Southampton for the development of NNPs in Wessex.

In planning this radical innovation it was felt that much could be learnt, and many problems possibly avoided, by examining the training and professional role of NNPs in North America. A study visit of six selected North American neonatal units and NNP training programmes was, therefore, undertaken by a group consisting of one paediatrician and four senior neonatal nurses. The two main aims of the visit were: (i) to study the NNP training programmes and (ii) to evaluate the clinical role of NNPs working in neonatal intensive care units.

Neonatal units visited

Details of all NNP training programmes in the USA were obtained from the National Association of Neonatal Nurses (NANN). There are approximately 30 such programmes in the USA and at least one in Canada, at McMaster University. Of these about 50% are certification programmes and 50% master's degree programmes. In addition at least one unit offers the opportunity for training at doctorate level. We decided to evaluate three master's courses and three certification courses (table 1). Identical information was collected from each unit and the following represents a synopsis of our findings.

Table 1 Neonatal units visited

Neonatal unit	*Type of programme*
Georgetown University, Washington DC	Certification
Samaritan College of Nursing, Phoenix, Arizona	Certification
St John's Mercy Medical Center, St Louis	Certification
University of Texas Health Sciences Center	Master's degree
Primary Childrens Medical Center, Salt Lake City, Utah	Master's degree
Rush University, Chicago	Master's degree/doctorate

(1) Origins of NNPs

NNPs seem to have been introduced into neonatal units in North America in the early 1970s. At about this time a formal study of the role development of the neonatal nurse was undertaken as part of a master's thesis by a nursing student.[4 5] This study is widely credited as forming the basis for the development of NNP programmes and the student who undertook the study, Patricia Johnson, is regarded by many as being the 'original neonatal nurse practitioner'.

Formal training programmes, however, did not become widely available until the early to mid 1980s. The introduction of NNPs was welcomed by many neonatologists in North America as being the only effective way of dealing with the ever increasing neonatal workload. Financially, there was clearly pressure on institutions to provide a neonatal intensive care service as this is a lucrative source of income for many hospitals; the introduction of NNPs has now provided an effective and reasonably economic source of skilled staffing for these units.

From the nurse's point of view there has been a widespread belief that extending the role of the neonatal nurse provides an effective, and at times superior, alternative to the variable standard and quality of care which relatively undertrained resident medical staff may provide. However, for this extended role to be acceptable to nurses of appropriate calibre it has been essential that in-depth training and education should be provided and that the new role should be seen by the profession as a genuine career advancement.

Although many courses have been initiated as certification programmes there has been a definite shift in emphasis from 'training' to 'education' and simultaneously a recognition that the nurse practitioner provides a different and possibly more holistic type of care than her medical practitioner colleagues. In recognition of these changes in role development and educational needs many programmes now award a master's degree after completion.

(2) Training programmes in North America

(A) DESIGN AND CONTENT OF THE COURSE

In order to be registered as qualified NNPs by the National Certifying Council (NCC) candidates must have successfully completed a certified NNP training programme and examination. The full time courses that we evaluated range in length from nine months to two years; in addition two centres offer part time courses that can extend up to five years. Most training programmes are jointly directed by a co-ordinator—usually a nurse with a master's degree—and a neonatologist. The courses are divided into a period of classroom based teaching (didactic) followed by a clinical apprenticeship (preceptorship).

A recent survey of existing programmes by the Special Interest Group of NANN found the minimum total course length to be nine months with at least 320 hours of theoretical teaching. This is then followed by the supervised clinical apprenticeship of at least 800 hours, which is usually undertaken in the sponsoring unit. The theoretical teaching includes the full range of neonatal medicine in a depth probably equivalent to that which would be covered by paediatric registrars during their training in this country. Lecturers include neonatologists, radiologists, physiologists, pharmacists, NNPs, and other specialists. Examples of the minimum number of didactic teaching hours are as follows: respiratory system, 38 hours; metabolic/endocrine system, 23 hours; and cardiovascular system, 20 hours.

In addition to the theoretical component, training in practical skills is provided for the procedures shown in table 2. It is the responsibility of the mentor to ensure that the student achieves a satisfactory level of clinical competence before graduation. Some units stipulate minimum numbers of procedures which should be successfully completed before qualifying. However, in some cases difficulties have been experienced when targets are set, but not achieved, before graduation. In these instances, the base unit is informed and this is highlighted as an area needing continued focus and attention after graduation. A variety of teaching aids and methods are used, including infant models and live animals (cats and rabbits); the latter are used in some but not all centres. The clinical apprenticeship is in all cases supervised by a neonatologist, but qualified NNPs are used as mentors and for role modelling and role development.

Table 2 Practical procedures

Procedure	*Minimum No required in some units*
Endotracheal intubation	10
Arterial sticks (stabs)	5
Suprapubic taps	5
Lumbar punctures	5
Chest drain insertion	3
Needle aspiration of the chest	3
Insertion of peripheral cannulae	None specified
Insertion of arterial cannulae	None specified
Insertion of umbilical arterial catheter	None specified
Insertion of umbilical venous catheter	None specified

(B) EVALUATION OF THE STUDENTS

All of the units visited use a combination of written examinations and clinical assessments. Many programmes also have weekly quizzes, case presentations, and project assignments. Clinical logs are widely used during the apprenticeship. Clinical evaluation of the students requires collaboration between the course co-ordinator, the student's mentor, and the neonatologist in charge of the unit in which the clinical apprenticeship takes place. Newly qualified NNPs are often teamed up with an experienced NNP or 'buddy' whom they work alongside for the first few months in their new role.

(C) FUNDING OF THE STUDENTS

Course fees and salaries are usually paid by the hospital in which the NNP student was previously employed. In many cases there is a formal agreement that, after qualification, the NNP will return to work in the sponsoring hospital for a specified period, usually two years. The incentive to become a NNP, however, is sufficient for some students to fund themselves during their training and most students accept a drop in salary while training. Students who are self funding often support themselves by working at weekends and during holidays.

(D) QUALIFICATIONS, QUALITIES, AND MOTIVATION OF THE STUDENTS

In order to be accepted onto a NNP training course students are usually required to have a minimum of two years' experience in neonatal nursing. In practice most student NNPs have at least four years' previous experience. Students are expected to be 'well above average academically' and a letter of recommendation is required from the neonatologist in charge of the student's base unit. Although personal interviews are not always held the following qualities are sought in potential NNPs: assertiveness, flexibility, leadership, communication skills, and the ability to handle stress.

For the experienced neonatal nurse the role of the NNP seems to offer autonomy, the ability to advance clinically and not into management, and the opportunity to acquire a more detailed understanding of neonatology.

(3) The role of the NNP

In most units NNPs are responsible to the fellow or attending neonatologists in their clinical role and to senior nursing colleagues in their educational role. It was reported by both medical and nursing staff that NNPs function at a level equivalent at least to a second or third year resident and, in some cases at the level of a fellow. Although the level of functioning of the NNP is equivalent to that of residents, prescriptions or orders are usually countersigned by medical staff within a set time. In most units, NNPs do not undertake the more traditional functions of staff nurses on neonatal units and it was suggested in more than one unit that it is not feasible for a highly trained NNP routinely to provide all of the nursing care required by sick neonates. However, it was stressed to us that a holistic approach is very important in the education of other members of the care team. In most units NNPs have their own caseloads—usually up to seven intensive care babies.

The NNP is expected to 'clerk in' patients, initiate appropriate management in conjunction with senior neonatal medical staff, and be responsible for the subsequent day to day clinical management. The NNP team often maintain responsibility for the babies they admit and are usually responsible for discharge planning. The working arrangements are variable and range from 10 hours each day, four days per week to a 24 hour on call system. In those units where 24 hour NNP cover is provided, it was reported that there is improved continuity of care and more job satisfaction. In more than one unit it was stated that NNP rotas are planned in conjunction with the medical rota, to ensure that if the medical staff cover is relatively inexperienced then a qualified NNP will be available on the unit. It was felt that this provides the best possible blend of experience. In most units the NNP teams are self scheduling and within their care teams they are expected to provide cover for each other if any problems with sickness or off duty requests arise.

The extent to which protocols are used varies from unit to unit, but it is generally accepted that they are used as guidelines only and should not be too detailed or prescriptive as legal problems may ensue if they are not followed exactly. In most units NNPs are involved in formulating both medical and nursing protocols which are usually endorsed by the neonatologist.

'Sharing of skills and considerable mutual support' was reported to be an important interaction between NNPs and residents, and although there is no formal role in teaching residents, it is generally accepted by the medical staff that NNPs do have an important educational role in ward teaching and they are seen as a vital resource for all members of the caring team. An awareness of potential difficulties in staff relationships was reported, particularly between NNPs and the other neonatal nurses; these problems are addressed during the training courses. However, it was unanimously reported by both doctors and nurses that NNPs have been welcomed by all members of staff and that no serious problems have occurred. We encountered no antipathy or jealousy between NNP and residents, who had seen their workload decrease and felt that they could learn from NNPs. Many staff nurses preferred NNPs to be responsible for the babies in their care as they felt there was improved continuity of care and they were able to learn from the NNP. From all areas the introduction of NNPs has been positively accepted and everyone spoke highly of their professionalism and the importance of their presence on the caring team. It was stressed that the role should be clearly defined from the outset, not only to help other staff nurses on the neonatal unit, but also to enable the recently qualified NNP find her new professional identity. One potential problem for trained NNPs is that they may be unable to maintain their skill levels if they work in nurseries with only limited intensive care facilities. To overcome this in some units NNPs working in level II nurseries rotated into level III nurseries and the NNP can also attend ward rounds in the intensive care units. Once qualified, almost without exception NNPs stay in the clinical area and the rate of attrition is very low. It is accepted that this is a job that nurses want to stay in for many years and that within the role there is scope for expansion, for example into clinical teaching or research.

The NCC have stipulated that NNPs should receive 45 hours of continuing education during each three year period to qualify for recertification. This may include attendance at weekly rounds (after prior agreement with the board of NCC) and attendance at local or national conferences and journal clubs. The provision of funding for attendance at national conferences varies from unit to unit: in some cases the hospital pay the full fees while in others up to 80% of the registration fees is paid but hotel accommodation and travel fees must be paid by the NNP.

Salaries are reported to range from $27 000—$70 000, teaching hospitals usually pay less than smaller units. Some units stated that initially there had been difficulties in obtaining increased funding for NNPs. This was thought to be due to the fact that most administrators and some nursing colleagues had no understanding of the extent of the role and the degree of responsibility it encompasses.

With regard to evaluation of the role there appears to be no consistency among the units. In some units the role is evaluated by the medical and nursing director and a peer review system, while in at least one unit staff nurses are required to provide a written evaluation of the NNP as a clinical resource.

(4) Legal implications

In all units legal indemnity is provided by the hospitals. It is the individual NNP's choice to decide whether or not to take out personal insurance but some institutions tend to discourage this on the grounds that this may complicate any legal proceedings. It was reported that some insurance companies are no longer willing to insure nurse-midwives or NNPs for personal liability. In stark contrast to litigation involving medical practitioners we were told by several senior members of NANN that there have been no known cases of litigation where a NNP has been cited.

Discussion

If the centres that we visited reflect the US in general there can be no doubt that the introduction of NNPs has represented a highly successful advance in the delivery of care to sick newborn infants—an advance that has been universally welcomed by both doctors and nurses. Moreover, in the pragmatic world of the privately funded health service which exists in the US, NNPs are financially viable because they enable hospitals to accept more patients, and therefore more funds, than would be possible if there were no NNPs. In contrast in the UK health system there is no such financial incentive to the introduction of NNPs. Indeed, many hospitals would regard any potential increase in patient load to be a good reason for not introducing NNPs as this would impose a financial burden on the institution.

Funding limitations certainly constitute an important reason for the inertia and relative indifference with which the concept of NNPs has so far been greeted in the UK but there has also been a widespread scepticism among neonatal nurses themselves concerning the advantages to the patient of extending the role of the nurse. There has been, therefore, no formal development of the extended role of the neonatal nurse in the UK and the visiting team had no previous direct experience of NNPs. With these considerations in mind we hope that the following observations will be regarded, not as criticisms, but as areas that we would hope to develop after the introduction of our own NNP training programmes.

It was implicit, although not always overtly stated, in most of the conversations that we held with both nurses and doctors that the care delivered by NNPs was undoubtedly superior to that of most first and second year residents and, in some cases, at least equivalent to that of third year paediatric residents and even fellows. This is hardly surprising given the negligible previous neonatal experience of most newly qualified doctors and the parsimonious allocation of time for neonatal training given to new residents in neonatology. The surprise, perhaps, lies in the fact that, in those hospitals in which NNPs and paediatric residents coexist, there remains such a well demarcated separation in the training of NNPs and residents. Having witnessed the impressive benefits afforded by the introduction of NNPs we feel moved to ask: why are paediatric residents in both the UK and the US still not accorded the benefit of a period of training equivalent to that of NNPs before they are required to assume a degree of clinical responsibility, and to undertaken intricate practical procedures, for which they are not adequately prepared? There are precedents for such periods of clinical training in the UK, notably in anaesthesia. Perhaps the answer lies in the financial implications involved in such a development.

In comparing the US with the UK there are important differences in medical staffing arrangements in neonatal units. First, the paediatric residents in the US—senior house officer equivalents—usually spend only one month at a time employed in the neonatal unit and, in accordance with recently revised guidelines, may receive a maximum of three to six months exposure to neonatology during their three year residency programmes. In contrast, paediatric senior house officers in training in this country are often employed continuously for six months and may spend longer at this level. Second, the clinical role of middle grade staff in the US—fellows—seemed to be less well defined in comparison to their UK registrar equivalents, particularly as there is now a requirement that fellowship programmes should emphasise training in research.[6] Finally the 'attending' neonatologist in the US tends to be more actively involved in the day to day running of the unit than his UK consultant counterpart, at least in many non-regional centres. There are also important differences in the training and functioning of neonatal nurses: there is no equivalent to the English National Board postregistration 405 course in the US and the training of staff nurses is probably less comprehensive than that of nurses who have completed the 405 course in this country. Such differences may be relevant to the way in which NNPs are incorporated into the UK system and it is possible that a different type of NNP may evolve in this country.

Since the original study conducted by Pat Johnson[4 5] there have been surprisingly few formal attempts at objective evaluation of NNPs to date,[7 8] although there are now plans for an assessment to be undertaken, involving at least three centres in North America. Here, we hope that we shall be able to benefit from the experience of our visit and to explore the possibility of evaluating the effect of introducing NNPs contemporaneously with their introduction.

In the light of the recent changes in the NHS funding mechanisms, the envisaged developments in the nursing profession and the imminent decrease in the working hours of junior doctors, the time has come to review the way in which care is provided for sick newborn infants and to begin exploring the potentially important contribution which 'neonatal nurse practitioners' may make in establishing a higher level and more consistent quality of care for newborn infants.

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Commentary

The concept of the neonatal nurse practitioner (NNP) has been the focus of much informal debate within neonatal units, with a wide variety of opinion and support for the concept obvious. It is apparent from listening to these discussions that a clear definition of an NNP does not exist. The major difficulty seems to be in confusing the extended role of the neonatal nurse with that of the NNP currently employed in neonatal units in the US and using the all embracing term of NNP to apply to both roles. The English National Board (ENB) describes the nurse practitioner as a nurse who has completed a course after basic training such as the ENB 405, and is encouraging development in curricula that includes extended practical skills traditionally associated with junior and middle grade medical staff, such as the siting of intravenous infusions, emergency resuscitation, and elective intubation. The emphasis is on practical competance rather than clinical diagnosis. This role would be more clearly defined as extended or expanded role. It appears within the grasp of current educational provision and established local management structures concerned with extended role nursing practices. The role of the NNP in the US describes the neonatal nurse functioning at a level similar to our middle grade medical staff, having a clinical caseload with responsibility for clinical diagnosis and management as well as extended practical competence.

Until these two clearly very different roles are recognised I feel there is a danger that local development will produce NNPs of varying levels of training and skill. This could compromise both medical and nursing staff as well as patients. The concept of an individual taking on a role of middle grade medical staff on a long term basis is an attractive one. The result would be an increase in depth of knowledge and practical skill and so would enhance the quality of neonatal nurse provision.

If this is the development neonatal nurses chose to pursue I feel it is imperative for a national body to be responsible for the standard of courses leading to this qualification. These courses should be at master's degree level, which implies a minimum of one year duration. This level of education is essential to equip nurses to function in this role. If no national body has control over courses, nurses could be placed in a position that makes them unemployable in any other neonatal unit outside those linked with their training institution. This would represent a waste of financial resources and place a severe restriction on nurses' career development and mobility. Consideration needs to be given to the increased nursing hours needed to make up the loss of nursing cover once provided by the new NNPs and that the workload of NNPs is not such that similar problems arise to those of the present junior doctors.

There does appear to be many highly motivated neonatal nurses keen to develop this role and the quality of neonatal provision would undoubtedly improve with the development of this role. Whichever professional group takes on this role a national initiative would seem the only way to ensure the strength of the concept surmounts this potential organisational weakness.

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CURRENT TOPIC

Vascular compromise in newborn infants

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With improved neonatal resuscitation techniques a number of infants are now surviving only to develop vascular problems secondary to intravascular catheterisation, repeated venepuncture, or arterial blood sampling. Spontaneous thromboses are also more common in early life than in later childhood.[1 2] Guidelines for the prevention, diagnosis, and treatment of blocked vessels in adult patients are not automatically applicable to the newborn. The size of the delicate vessels, the immature haemostatic mechanism, and the background of relative polycythaemia pose special problems.

Thromboembolic vessel obstruction may result in death or irreversible damage to an organ or limb. In addition to blockage of peripheral vessels,[3 4] thrombosis of the cerebral,[5] pulmonary,[6 7] coronary,[8 9] renal,[10] and mesenteric arteries,[11] is reported in the neonate. Peripheral artery occlusion usually presents with a cold, pulseless, mottled, and discoloured limb. Obstruction of the central veins or arteries may be more difficult to recognise. Renal vein thrombosis, for example, does not always present with haematuria and an enlarged kidney, and thrombosis of the aorta may not disclose itself with congestive cardiac failure and ischaemia of the lower limbs.[1]

Incidence

The incidence of thrombosis in the newborn appears to be increasing.[12] This may be due to more widespread use of intravascular catheters, prolongation of life in very ill infants, or a more careful analysis of necropsy material where previously the diagnosis of vessel thrombosis was missed.

Cannulation of the umbilical vein is particularly associated with thrombosis. Postmortem examination of infants revealed thrombotic complications of umbilical vein catheterisation in between 20 and 61% of cases, although in some of them the infusion of a hyperosmolar solution may have been a factor.[13 14] Umbilical artery cannulae have also been shown frequently to cause thrombosis both on necropsy studies[15 16] and on aortography.[17] Of course, not all the reported thromboses would have led to ischaemic damage. In some cases the vessel is only partially occluded and in others an adequate collateral circulation exists. In a large series of 4000 patients with umbilical artery catheters, only 1% developed actual clinical symptoms of thrombosis.[18]

The placement of vascular catheters carries a potential risk no matter which vessel is involved. Neonatal thrombosis has been described in association with radial,[19] femoral,[20] pulmonary,[21] and temporal artery[22] lines, as well as with catheters into the jugular[7 23] or femoral[24] veins. Thrombi are also found when catheters are not used. A review of consecutive necropsies revealed a 4·5% incidence of thrombosis in uncatheterised cases, and an 11% incidence when intravascular catheters were used.[25] Even temporary catherisation can cause problems. In a prospective study of children undergoing cardiac catheterisation, 3·6% developed clinical symptoms of femoral artery thrombosis.[26] An extensive literature review of 1045 cannulations of the radial artery in newborn infants showed that 6% of cases suffered transient ischaemia and 0·5% had permanent ischaemic damage.[27] Even hand amputation after radial artery cannulation has been reported.[28] The incidence of vessel occlusion without ischaemic changes, however, is as high as 63%,[29] and in such cases, an adequate collateral circulation exists. Flow in the blocked vessel is often restored several days after catheter removal.

The propensity to develop thrombosis is related to size of the infant. The risk of vessel obstruction after cardiac catheterisation is highest in infants of less than 10 kg.[27 30 31]

Aetiology

The cause of thrombosis in the neonatal period is often uncertain but some key factors bear special mention. It is mainly sick children who are affected. In one early series, 80% of cases were associated with infection. One factor here may be the growth of small endocardial vegetations which dislodge to occlude distant vessels.[4] Emboli may also derive from cardiac thrombi secondary to fibrillation and anomalous valves.[4]

Some maternal factors are important. Both venous thrombosis and peripheral gangrene have been reported in the infants of diabetic mothers.[32–34] Venous emboli may pass through the foramen ovale to enter the arterial circulation.[34]

Thrombus formation in fetal placental veins is unusual in a normal pregnancy, but occurs quite often in maternal hypertension.[35] Chorionic thrombi may embolise to fetal vessels and have been linked to the presence of pulmonary and portal venous emboli.[35] In cases of initial twin pregnancy with subsequent fetus papyraceous of one, fragments of thromboplastic material may pass through vascular shunts to the circulation of the live fetus,[36] to present as local ischaemic damage due to thrombosis.[36–38] It is estimated that 32% of pregnancies which are twin at 10 weeks lead to singleton deliveries.[39] Thrombi may also form within a patent ductus, particularly when there is an aneurysmal dilatation,[40] and resulting emboli can cause peripheral vessel occlusion.[4]

Virchow postulated three major factors contributing to the formation of thrombi: abnormalities of the vessel wall, disturbances of blood flow, and changes in blood coagulability.[41] This provides a convenient framework within which to examine how neonatal thrombi may form.

(1) ABNORMALITIES OF THE VESSEL WALL

If during birth a limb is trapped between the fetal head and the maternal pelvis, damage to the intima of a major vessel sufficient to precipitate thrombosis may occur.[4 42] Birth trauma may explain some cases of limb ischaemia but thrombosis has also been seen after caesarean section,[43] in association, for example, with amniotic construction bands[43] and entrapment by the umbilical cord.[42]

External pressure on the vessel wall due to a compartment syndrome has been reported to cause vessel obstruction and digital ischaemia; fasciotomy was beneficial.[44] Even drugs extravasated into the subcutaneous tissues during emergency neonatal reconstruction can obstruct the venous return of an upper limb, and removal of the offending material by aspiration using blunt cannulae can restore the circulation (D T Gault, personal observation).

Thrombosis of femoral vessels leading to amputation after venepuncture has been reported.[45] Intentional and inadvertent arterial puncture is also known to cause arterial thrombosis,[46] especially if a substance which irritates the vessel initima is infused.[47] Even a vasculitis in a newborn infant has presented with peripheral gangrene.[48]

Intravascular catheters can act as a nidus for fibrin and platelets, may damage the endothelium of the vessel wall, may partially occlude a vessel, and may precipitate vasospasm. Neonatal monitoring with umbilical artery catheters, introduced in 1962,[49] is now commonplace and is associated with the majority of catheter related thrombosis. The risk is greatest when hyperosmolar solutions are infused.[26]

(2) FLOW

Hyperviscosity of the blood is reported in 1–5% of neonates.[50–52] Blood viscosity is a function of plasma viscosity and packed cell volume. In newborn infants, a venous packed cell volume greater than 0·65 is considered to be indicative of hyperviscosity; a small rise in packed cell volume above 0·70 results in a considerable increase in blood viscosity.[52] Delayed cord clamping can increase packed cell volume by permitting extra placental blood to be transferred to the infant. Hyperviscosity is also related to the deformability and aggregability of the red blood cells—those of a newborn infant are larger and less deformable than in older children and are associated with increased platelet adhesion.[53]

Increased blood viscosity is noted in the infants of smokers[54] and diabetic mothers[55] where sluggish maternal circulation may cause compensatory polycythaemia in the fetal blood. Small for dates babies are also prone to polycythaemia and in them this may be a response to chronic hypoxia as a result of placental insufficiency.[50] Hyperviscosity adversely affects blood flow leading to a relative local hypoxia and acidosis which may prematurely trigger the coagulation system.[56] Peripheral gangrene in a term infant with polycythaemia has been reported.[57]

The risk of arterial and venous thrombosis is high in dehydrated infants, usually those with neonatal diarrhoea.[4 33 57–61] The newborn have little reserve to cope with dehydration, and an extracellular fluid volume deficit rapidly leads to a low flow state that could aggravate a tendency to thrombosis.[46]

(3) COAGULATION

It is currently thought that damage to the vessel wall and disturbances of blood flow are more directly implicated in neonatal thrombosis than the peculiarities of neonatal haemostasis and fibrinolysis.[1] In a healthy infant both the coagulation and fibrinolytic systems are immature but in balance. Inherited deficiencies of antithrombin III[62] and protein C[63] have been reported in neonates and were associated with fatal thrombosis.

Treatment

Neonatal intensive care units are likely to encounter vascular compromise and should formulate a treatment policy. Even when arterial occlusion does not cause irreversible ischaemia, the affected extremities may suffer retarded growth.[64–66] The small calibre of the vessels, their tendency to spasm, and reports of rethrombosis after surgery have in the past curbed enthusiasm for a surgical solution. However, with recent advances in microsurgical techniques, some success has been recorded.

HEPARIN

The newborn infant appears to require a proportionally larger amount of heparin than an adult to achieve an adequate therapeutic effect and as the half life is short, continuous infusion is the best method of treatment.[67] A 50 unit/kg bolus followed by 20 units/kg/hour has been shown to resolve femoral artery thrombosis after cardiac catheterisation in 43% to 80% of cases.[67–69] McDonald and Hathaway showed that a mean dose of 27 units/kg/hour was required to give plasma heparin concentrations in the therapeutic range (0·3–0·5 units/ml) and they reported good results in 14 out of 15 babies studied.[67]

THROMBOLYSIS

Thrombolytic treatment has been shown to be effective and safe in a paediatric population.[26 68 70] Two thrombolytic agents, streptokinase and urokinase, are widely used to activate plasminogen which is converted to the proteolytic enzyme plasmin, capable of dissolving fibrin clots. Administered systematically, these drugs can treat both arterial and venous thromboses, but there is a risk of haemorrhage, especially in preterm babies who already run a high risk of intracranial haemorrhage.[71] Clots less than five days old are more susceptible to thrombolysis,[70] but chronic obstructions have also been treated.[72 73] A loading dose of 10 000 units/kg of streptokinase and then 1000 units/kg/hour is recommended.[68] The treatment is then adjusted to reduce fibrinogen concentrations to between 1·0 and 1·4 g/l. If little response is noted, streptokinase can be increased to 2000 units/kg/hour. Streptokinase is made from the streptococcus, and may be affected by the presence of antistreptococcal antibodies; urokinase is considered by some to be preferable as it is non-antigenic. A loading dose of 4000 units/kg of urokinase followed by 4000 units/kg/hour[68 74] has been commonly used but some authors have doubled the loading dose[75] or the hourly infusion rate.[76]

The fibrinolytic mechanism is not fully developed at birth, and a bias of the haemostatic mechanism towards fibrin formation has been reported.[77] Like heparin, a higher concentration of the plasminogen activator may be required for successful thrombolysis in the newborn and premature infant relative to older children and adults.[78 79] Corrigan *et al* showed that 11 times the amount of urokinase was required to achieve levels of activity seen in adults.[79]

Many authors have reported success with thrombolytic treatment. In heparin resistant femoral thrombosis, thrombolysis was successful in excess of 85% of cases.[26 68 78] Thrombolysis has been recommended as the first line treatment for thrombosis, with thrombectomy reserved for those that do not respond.[80] Local administration at the site of the blockage using a catheter permits lower doses to be used.[81] Selective treatment with 50 units/kg/hour of streptokinase has shown good results in children.[70 82]

SURGERY

Thrombectomy in very young infants is prone to reclotting[83] but despite this, useful limb salvage is often achieved.[83–86] The passage of a Fogarty catheter down a small vessel may fissure the intima,[86] and even mobilising a vessel has been reported to cause thrombosis in this age group.[87] Flanigan *et al* noted that very small (2–3 French gauge) Fogarty catheters could not enter the femoral arteries of a neonate.[88] Clots may, however, be removed by aspiration using a small plastic catheter with a blunt end.[46 87] Both success[3 46 69 86 89–91] and failure[92] of thrombectomy is recorded.

The femoral and brachial arteries in neonates are of a similar size to the digital vessels in adults where microsurgical replantation surgery is now routine. Even when thrombectomy from such vessels does not restore all pulses, the limb is often salvaged and the surgery may well improve access to the collateral circulation. In one recent case where persistent rethrombosis beset a surgical reconstruction in a preterm infant, the limb was salvaged using postoperative thrombolytic treatment.[85] Surgery to salvage a failed trial of thrombolysis, and thrombolysis to improve the results of surgery may yet provide the most comprehensive treatment option. Even when a limb is viable after a thrombosis, there may be later growth discrepancy. Surgery, when the child is older, has been described to improve limb blood flow and equalise limb length.[65 69]

Complications

Vascular occlusion can precipitate distal ischaemic damage and necrosis, but even when an adequate collateral circulation develops, a variety of late complications can occur. In the upper limb, contractures and stunted forearm bone growth have been reported.[93] Damage to the femoral artery after cardiac catheterisation has also caused reduced leg growth[64–66 88] and some children have even gone on to develop claudication.[83]

Prevention

Catheter related vascular occlusion is likely to be influenced by the type of catheter, its placement, and the concomitant use of heparin. The use of smaller catheters for cardiac catheterisation has decreased the incidence of femoral artery thrombosis.[26] Heparin as a 100 unit/kg bolus at the time of catheterisation has also reduced the incidence of thrombosis in these children.[94] Low dose heparin (1–2 units/ml in infusions) has been shown to prolong umbilical artery catheter patency,[95] but may not affect the thrombosis rate.

Silastic catheters are less thrombogenic than standard polyvinyl chloride catheters[96] and end hole catheters are less thrombogenic than side hole catheters.[97] The use of thromboresistant umbilical artery catheters (heparin bonded to the surface polyurethane) failed to reduce the incidence of complications significantly.[98] The thrombosis rate is not affected by a change in the placement of the catheter tip, either at the seventh thoracic or fourth lumbar segment.[99]

Conclusion

Vascular compromise in a neonate was first described in 1828 and of the first 52 cases of ischaemic extremities, 17 died and 17 lost limbs.[43] Much better results are now obtained. Early recognition of the problem with prompt instigation of thrombolytic treatment has become the mainstay of treatment. Good results of surgical thrombectomy are also now recorded, and once again, early referral is essential. While rethrombosis after surgery may occur, the unconventional combination of surgery and subsequent thrombolytic treatment has salvaged limbs in very difficult circumstances.[85]

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Commentary

Severe examples of ischaemic limb damage, especially those culminating in amputation, have probably become less common as a result of increased vigilance for early signs of ischaemia, better catheters and related equipment, and improved skills of the operators. None the less, the rising population of extremely preterm babies are a vulnerable group and fear of retinopathy may lead to determined attempts at arterial oxygen monitoring by sampling through an arterial catheter or by repeated arterial puncture.

A range of physical signs may be observed which suggest limb ischaemia including mottling, blue discoloration, blanching, poor capillary refilling, coolness, and poor pulses. Often these signs are transient but sometimes they progress to frank gangrene with a demarcation line.

Mr Gault's informative and well referenced paper indicates the spectrum of treatments available, including the scope for surgery. A major difficulty for paediatricians is that there is still insufficient information derived from clinical studies to decide the appropriate management in individual circumstances, especially in extremely small babies. When signs of limb ischaemia are first observed we usually do not know whether they are due to reversible arterial 'spasm', thrombosis, or embolism. Dextran, heparin, streptokinase, and urokinase have risks in very small ill babies. Neonatal care is about balancing risks but we are hampered if neither the risks nor the benefits are understood. Finally, most paediatricians won't have ready access to a surgeon with experience in microsurgery—such experience that there is being embodied in single case reports.

Faced with these uncertainties the best approach is firstly to avoid unnecessary harm. A perceived risk of retinopathy is no reason to strive for arterial access *at all costs*. When invasion of arterial territory is contemplated there is always room for considering the alternative monitoring strategies. It would seem sensible to correct polycythaemia, hypovolaemia, and hypotension before arterial catheterisation, bearing in mind that these factors predispose to vascular compromise. Hyperosmolar solutions should not be infused through arterial catheters, and increased vigilance is required in babies receiving vasopressor drugs. The catheter should be promptly removed if signs of ischaemia, including early blanching, develop. It should not be replaced at the same site even if the signs regress.

The litigation implications of vascular compromise should be acknowledged. Medical and nursing staff must be protected from blame when there was no negligence; but we must also protect a patient's right to compensation where the standard of care was unreasonable. Accurate documentation in the medical and nursing records of events in relation to arterial catheterisation is a basis for the fair assessment of claims.

Arterial catheterisation, including unsuccessful attempts, should be noted and the time recorded. The same applies to arterial punctures—timed information on the blood gas chart is acceptable provided the site of the arterial sample is given. When an arterial catheter is in use a measurement of the adequacy of the circulation in the appropriate limb should be recorded at hourly intervals in the intensive care chart—for example, 'warm and pink'. Signs consistent with ischaemia should be recorded and timed. If, as a result, a catheter is removed then the time of removal must be noted. The progression or regression of ischaemic signs should be recorded along with the timing of any treatments.

In practice, a careful attitude towards documentation usually goes hand in hand with clinical vigilance and against this background avoidable vascular compromise is less likely to occur.

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PERINATAL LESSONS FROM THE PAST

Scevole de Ste Marthe of France (1536–1623) and *The Paedotrophia*

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Scevole de Ste Marthe was born in Loudun, France, in 1536. He studied law, first at the University of Paris, and then at the University of Poitiers where he settled, married, and successively became Mayor, Governor, and then President of the District.[1] Besides being a lawyer, he was also a fine poet. Although not a medical man, his most famous work, *The Paedotrophia*, was a Latin poem in three books on pregnancy, childbirth, and the care of infants. It was first published in 1584 and was reprinted many times over the next two centuries. Henry III of France, to whom the poem was dedicated, requested him to translate it into French; it was also translated into English, first in 1710, and then again in 1797 by Dr Tyler, a medical practitioner in Forfarshire. It is from this second translation that the extracts that follow were taken.[2]

Scevole de Ste Marthe first developed an interest in the care of infants when two of his own children became seriously ill and died of smallpox. He describes the occasion poignantly:

> 'When they, by violence, bring from within
> A load of pustules on th' inflaming skin,
> That, with unnumber'd wounds, deform the face,
> And ev'ry issue of the soul oppress.
> By this (Oh! sad remembrance, fatal tale!)
> To me two beauteous infants lately fell:
> Four summers o'er my lovely Charles had run,
> And thrice Diana saw the annual sun,
> But, ere the next, from me, and from my spouse
> Were snatch'd the double honours of our house.
> Ye mighty Gods! if love for man remain,
> And all a Poet's pray'rs be not in vain,
> Save the delightful pledges of our bed,
> That yet survive, from these dire ills that shed
> Destruction round; avert th' infectious woe,
> Nor wound our peace by a succeeding blow'.

After this experience, as his biographer Gabriel Michel wrote in 1629, 'he was not sparing of the experience and care of the best physicians; he applied himself likewise to search curiously the natures and constitutions of infants . . . His researches (were) so successful that he cured his young son by remedies of his own prescribing after he was given over by the physicians. Being then entreated by his friends to communicate such curious discoveries to the public he comprehended them in this poem'. It brought him fame. *The Paedotrophia* was studied throughout the universities of Europe for the next 200 years with the same veneration as was accorded to works from classical times. Not only was it the first post-renaissance tract on infant care but it abounded with sound commonsense and practical advice:

Diane de Poitiers (1571) with her infant and wet nurse.

> 'Teach me to sing, how Infants should be fed,
> How nurs'd, how cloth'd and from the cradle bred,
> While their weak nerves, and tender frame, demand
> The softest care of an attending hand'.

Scevole de Ste Marthe deplored the fashionable practice of farming infants out with wet nurses (figure) and extolled the virtues and pleasures of breast feeding and motherhood:

> 'Then, if her breast maternal love contain,
> Nor o'er her mind unnat'ral darkness reign,
> She sure will feed the pledge herself, nor curse
> The crying infant with a venal nurse;
> Whose foreign blood but ill the want supplies
> Of what th' ungrateful mother now denies:
> What tenderness can o'er from her be known,
> Who, for another's child, neglects her own?'
>
> 'But you perhaps, by other cares beguil'd,
> Wish, to the nurse's house, to move the child;
> Because, by his continu'd cries at home,
> Your sleeps are broken, and your joys o'ercome.
> But if or love, or tenderness, be left
> Within your mind, nor you of good bereft,
> Of the forsaken babe take so much care,
> Yourself to see him plac'd in proper air;
> Nor be the needful charge to others giv'n,
> To guard him from th' inclement blasts of heav'n'.
>
> 'Blest is the Mother, from such errors free,
> That her own image, in her Child, can see;
> Whose breast maternal cares alone can move,
> Who finds her duty center'd in her love,
> Obeys her husband, slights all foreign charms,
> And breeds her infant in her parent-arms'.

'A Sage declar'd, and with the speech I'm pleas'd,
No Mother, should from nursing be releas'd,
But freely give what oft she keeps with pain,
And let her Child the snowy fountains drain . . .'

'But when the child within the craddle lies,
Demanding aid with tears, and melting cries . . .'

'To sooth his soft complaints, the mother fly,
And bring the tempting breast before his eye,
Advance the nipple to his op'ning lip,
And give him still th'ambrosial juice to sip,
Then, strange to tell, new pleasure fill his mind,
And calm his griefs, and mingle with the wind? . . .'

'Spontaneous still the grateful liquor glides,
And still the child sucks in the flowing tides,
Attempts with hands and mouth the breast to seize,
And drains the kindred juice, and lies at ease . . .'

There is useful advice on the technique of breast feeding and on weaning:

'But, at the first, while small and weak his jaws,
Balk not his hopes, when he the nipple draws;
But squeeze your breast with gentle pressure still,
And bring him close, and give the child his fill.
Yet let him not, too much, the fountains drain;
Sometimes indulge the feast, sometimes restrain;
Just at his mouth the nipple take away,
And raise his hunger by a short delay . . .'

'And I, for suckling, no fix'd hour prescribe;
This Nature teaches best the nursing tribe:
Let her your mistress be; and when, with cries
The hungry child demands his due supplies,
Forbear not you the wish'd relief to bring,
But, for his use, unlock the sacred spring;
Nor then be loth your snowy breast to bare,
That he may suck, and streaming fragrance share . . .'

'But, in short time, the growing babe will need
Not on th' ambrosial juice alone to feed.
When twice four times the moon has fill'd her orb,
And shooting teeth the swelling gums disturb,
Restrain the flowing feast . . .'

'When now you change, and give but half the breast,
Food, most resembling milk, is still the best:
Nor is it good too suddenly to use
Viands, quite diff'rent from the kindred juice,
Unless you know their nature to correct,
And form the medium his desires expect'.

Ste Marthe attached great importance to avoiding both chilling and over heating of the newborn infant; in particular he warned against bathing in cold water.

'Remember too, that only, by degrees,
His tender skin endures the cooling breeze:
Expose not, recent from the womb, the child,
Except to gentle heat, and seasons mild;
Lest ills succeed, lest penetrating cold
Benumb his limbs, and of his joints take hold . . .'

'A craddle soft and well-prepar'd he needs;
There lay him down, and, while he rests, take care,
You neither make too cold nor hot the air:
From cold will coughs and rheumatisms spring,
And heat indulg'd exhausted spirits bring.
Extremes in ev'ry case are wrong, and must;
Still in a medium you more safely trust:
But this few female minds have known to use,
And ev'ry liberty are apt t' abuse.
Misguided fondness makes our nurses err
By heating infants, and excluding air,
Hence are their limbs relax'd, their spirits weak;
Hence oft the thread of life itself will break;
And thus the widow'd mother vainly mourn
Her blested hopes, that can no more return'.

The Paedotrophia contains plenty of advice much of it sound, on such matters as the care o the umbilical cord, tongue tie, teething, an bowel problems. There is also advice to th mother on the antenatal care of her child, an on the conduct of labour and delivery:

'Then, when the nine revolving moons are run,
When now the long-expected hour comes on,
Invoke Lucina's aid, with potent voice,
And let a skilful midwife be your choice;
That death, nor danger, may the birth attend,
But former pains in coming pleasures end.
Let her, with hand and voice, assist your throes,
With oft-repeated touches soothe your woes . . .
Then, whether on a bed your limbs repose,
Or in a chair you wait the coming throes,
(For either way is good), be not dismay'd,
Nor of the fiercest pain at all afraid;
Let not your strength of mind to these give way,
But conquer still, less you the birth delay.
If, in your limbs, such vigour yet remains,
Stand up, for standing will assist your pains . . .

But cease not you, your weary'd limbs to spread,
To bend your knees, or on the chair, or bed;
And grasp some strong support with all your pow'r,
T'increase your efforts in that painful hour'.

'But now the helpless infant leaves the womb,
That, nine long moons, had been his living tomb;
And, as the sign of our first mother's sins,
With cries, and soft complaints, his life begins.
Then you, to whom the tender cares belong,
Or maids, or nurses, round the child-bed throng,
Make haste; and since both wife and infant claim
An equal succour, let them find the same.
While, for the wearied mother, some prepare
The bed, let others make the child their care,
In cloths well-warm'd involve his tender limbs,
And, for the bath, infuse the tepid streams
In proper vessels; some the cradle make,
And all the house in joyful toil partake'.

Scevole de Ste Marthe lived to be 87. He died in 1623 and was buried in the Cathedral at Loudun, his birthplace. His epitaph described him as '*Pater Patriae*'.

1 Still GF. *The history of paediatrics*. Oxford: Oxford University Press, 1931.
2 Ste Marthe S de. *Paedotrophia or the art of nursing and rearing children*. 1584. Translated from the Latin by H W Tyler. London: Nichols, 1797.

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LETTERS TO THE EDITOR

Cerebral blood flow velocity changes after rapid administration of surfactant

SIR,—We enjoyed reading the paper by Dr Cowan *et al*,[1] but we have a number of problems in relating the findings to the conclusion of the authors. The rationale behind the study appears to be the finding of an increased incidence of severe intraventricular haemorrhage in one study of surfactant replacement.[2] The authors do mention two other randomised trials which reported a reduction of intraventricular haemorrhage, to which one might add a further two[3] (this review lists four studies, references 37–40, which demonstrate significant reduction in intraventricular haemorrhage after surfactant treatment). Large intraventricular haemorrhages of grade III and IV have also been shown to be reduced in four studies[3] (references 37, 39, 50, 51).

A meta-analysis involving 34 randomised controlled trials shows odds ratios (95% confidence intervals) for the effect of surfactant on intraventricular haemorrhage of 0·89 (0·73–1·07) for prophylaxis and 0·79 (0·64–0·97) for rescue studies.[4] The body of scientific evidence points to a modest reduction of intraventricular haemorrhage after surfactant treatment.

The authors go on to say that the collaborative European multicentre study of Curosurf found a surprisingly high incidence (26%) of severe intraventricular haemorrhage, but they omit to say just how ill these infants were, as they required mechanical ventilation in $>60\%$ oxygen within the first 15 hours of life.[5] Indeed the control infants had a mortality rate in excess of 50%. The incidence of severe intraventricular haemorrhage in this study is less than that reported in at least three other studies[3] (references 54, 58, 67) using rescue surfactant.

Many of the babies studied by Cowan *et al* would not have fulfilled the criteria for the collaborative European multicentre study of Curosurf[5] as they were treated up to the age of 72 hours. The authors do not say whether any of their infants suffered from severe asphyxia, although we are told that the infants had pancuronium and pethidine. It seems likely that these babies were extremely ill and in the discussion it is said that seven out of eight had poor or absent cerebral autoregulation.[1] The authors correctly point out that there was a modest reduction in mean arterial pressure after giving surfactant and on looking at their results it would seem that in some infants mean arterial pressure and cerebral blood flow velocities (CBFV) actually increased. The levels of mean arterial pressure in the graphs all appear to be above 30 mm Hg which is a level at which the authors had previously noted an increase of cerebral lesions.[6] The authors do not report the rate of intraventricular haemorrhage in their babies nor demonstrate any relationship between the reduction in either mean arterial pressure or CBFV and the severitiy of intraventricular haemorrhage. CBFV may not reliably reflect cerebral blood flow (CBF) when heart rate, blood pressure, carbon dioxide tension, and cerebral vessel diameter may all be changing. CBF measured using 133 xenon clearance (G Greisen and A Bell, personal communication) and near infrared spectroscopy (EOR Reynolds and AD Edwards, personal communication) shows no consistent change after Curosurf administration and is related to change in carbon dioxide tension.

The final paragraph of the discussion again suggests that there is a relationship between surfactant treatment and increase in intraventricular haemorrhage where in fact none exists. The reduction in intraventricular haemorrhage is in keeping with our two year follow up studies with Curosurf which show that 80% of treated survivors have normal development compared with 72% of control infants.[7] We are aware of only one study which has looked at a slow continuous infusion of Curosurf compared with the currently recommended bolus instillation. In this pilot study the improvement in blood gases was less and the duration of effect greatly shortened. (PW Nars and C Rudin, personal communication). Perhaps there is a need for larger randomised trials of different methods of surfactant instillation or perhaps the haemodynamic changes reported by the authors were due to compromise of their infants before treatment or to their concomitant drug treatment.

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Dr Cowan et al comment:

We appreciate the interest in our paper expressed by Drs Halliday and Robertson. Nowhere in our paper do we state that a consistent association has been shown between surfactant treatment and intraventricular haemorrhage (IVH). While a number of randomised trials have shown a reduction in IVH, Horbar's multicentre trial with 106 infants randomised found 38·5% of surfactant treated in infants developed severe (grade 3 or 4) IVH against 15·4% in the control group ($p<0·01$).[1] In the collaborative European multicentre study of Curosurf slightly more infants developed severe IVH in the surfactant group than in the control group (no statistical significance).[2] As surfactant treatment has consistently been shown to lower mortality it is extremely important to ensure that this is not at the expense of increased survival of infants brain damaged by haemorrhage or ischaemia. Thus we felt that more investigation of the changes in the cerebral circulation with bolus surfactant administration was needed.

All the infants we studied would have qualified for the collaborative multicentre study of Curosurf on all criteria. The infants were extremely ill, but these are precisely the infants most at risk of cerebral lesions and where physiological information is needed. Pancuronium and pethidine were used to prevent 'fighting the ventilator'. These two drugs are known to have a stabilising effect on blood pressure.[3] Thus it is difficult to follow the suggestion that the haemodynamic changes could be due to these two drugs rather than the surfactant. We did not relate changes in blood pressure to scan findings as the numbers were too small for statistical significance. We agree that velocity measurements may not always reflect flow but our findings of a change in spectral pattern to one with low or absent end diastolic velocity suggests changes in flow pattern that may not be detectable by the other methods cited. We look forward to reading about the effects of slow continuous infusion of Curosurf.

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Gastroduodenal perforation in preterm babies treated with dexamethasone for bronchopulmonary dysplasia

SIR,—We read with interest the recent paper by Dr Ng and colleagues[1] and would like to add a comment on prostaglandins. The authors did not refer to gastric prostaglandins in patients and prostaglandins in maternal breast milk, but these substances may play an important part in the aetiology and treatment of gastroduodenal mucosal lesions and perforation in preterm babies treated with dexamethasone.

Prostaglandins, and PGE_2 and PGI_2 in particular, are known to regulate protective factors in the gastroduodenal mucosa such as mucosal blood flow, mucus production, and bicarbonate secretion. A decrease in prostaglandins in the gastroduodenal mucosa will therefore result in the depression of the protective mechanisms, thereby contributing to the development of gastroduodenal mucosal lesions. On the other hand, glucocorticosteroids are known to inhibit prostaglandin biosynthesis through the suppression of phospholipase A_2 activity. Nobuhara *et al* have shown that prednisolone reduces PGE_2 and 6-keto $PGF_{1\alpha}$ in the gastric mucosa and have demonstrated a good correlation between this decrease and the development of gastric mucosal lesions.[2] We have also demonstrated an impaired increase in PGE$_2$ in gastric juices which is thought to reflect the amount of PGE$_2$ in the gastric mucosa during steroid treatment in children.[3] Moreover, Marino *et al* have reported that the PGE$_2$ concentration in the gastric secretion in premature infants was significantly lower than that in full term infants.[4] On the basis of these findings, we suggest that a decrease or impaired increase in PGE$_2$ in the gastroduodenal mucosa is one of the important factors in the development of gastroduodenal mucosal lesions and perforation in preterm babies treated with dexamethasone.

This suggestion may have a therapeutic implication when it comes to breast feeding, although Ng *et al* described it in only one of four cases. The administration of oral PGE$_2$ analogues has been shown to protect the gastric mucosa from steroid induced damage.[2] In addition, a considerable quantity of prostaglandins including PGE$_2$ has been identified in human milk but not in infant formulas.[5] Consequently, breast feeding may have an important protective effect on gastroduodenal mucosal lesions in preterm infants during steroid treatment.

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The prophylactic use of ranitidine in babies treated with dexamethasone

SIR,—The Collaborative Dexamethasone Trial Group recently reported an increase in gastrointestinal bleeding among dexamethasone treated preterm infants compared with controls, although this did not reach statistical significance.[1] This trial did not report any babies with gastrointestinal perforation but two recent papers in this journal estimated an incidence of perforation of the order of 2–3%, and it was associated with considerable morbidity and mortality.[2 3]

The mechanism by which steroids cause gastrointestinal ulceration is unclear, although it is generally accepted that they reduce the effectiveness of the protective mucosal barrier. In this situation normal acid production may be sufficient to cause gastrointestinal perforation. Since we noted this complication we have tried to reduce acid production, with the H$_2$ receptor antagonist ranitidine, in all babies treated with steroids. To determine the effectiveness of this practice we have been serially monitoring gastric pH in babies treated with dexamethasone and various doses of ranitidine.

We report the effects of using a ranitidine infusion of 0·0625 mg/kg/hour in seven babies treated with dexamethasone and not receiving enteral feeding. Patient characteristics and results are presented in the table. This dose of ranitidine caused a significant increase in gastric pH ($p<0·0001$).

The characteristics and results of the patients studied

	Gestation (weeks)	*Weight (g)*	*pH before ranitidine*	*pH while on ranitidine*
Mean	27·7	849	1·7	4·9
Range	24–31	579–1171	1·3–2·0	4·2–6·0

In order to test whether or not the routine use of an H$_2$ antagonist would significantly reduce the incidence of gastrointestinal bleeding or perforation due to dexamethasone a controlled trial involving more than 2000 babies would have to be performed. Although this would be desirable, as it would allow adverse as well as beneficial effects to be looked for, it is unlikely to be done. In the meantime, because of its demonstrated effectiveness in reducing gastric acid secretion, we currently administer ranitidine prophylactically to all babies treated with dexamethasone.

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Non-invasive assessment of pulmonary arterial pressure in healthy neonates

SIR,—Recent correspondence in this journal referred to the assessment of pulmonary artery pressure by Doppler using the ratio of time to peak velocity (TPV): right ventricular ejection time (RVET).[1] We should like to point out that the position of the regression line relating TPV:RVET to pulmonary artery pressure is influenced by whether the pulsed Doppler sample is taken from the *right ventricular outflow tract* proximal to the pulmonary valve or from *the main pulmonary artery*. If TPV: RVET, measured from the main pulmonary artery, is plotted on a regression line derived from measurements made in the right ventricular outflow tract then an inappropriately high mean pulmonary artery pressure will be obtained. This explains why Skinner *et al*, commenting on our letter,[1] found an impossibly high pulmonary artery pressure of 100 mm Hg when they plotted our measurement of TPV:RVET (sampled from main pulmonary artery) on a regression line based on Kitabatake's measurements (sampled from right ventricular outflow tract).[2]

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Respiratory support using patient triggered ventilation in the neonatal period

SIR,—I should like to comment on your recent timely article on patient triggered ventilation in the neonatal period.[1] The authors indicate that in a recent study patient triggered ventilation (PTV) was successful only in three out of 16 infants with chronic lung disease because of asynchrony or poorly sustained respiratory effort in these infants. It may be more appropriate to use a longer inspiratory time (0·6 seconds) when ventilating these babies in trigger mode as this has been shown to be associated with an increase in tidal volume due to recruitment of more collapsed alveoli.[2] Similarly, if such an infant is being weaned using PTV, doing so by decreasing peak inspiratory pressure may result in progressive alveolar collapse. We have recently had difficulty weaning an infant with chronic lung disease in this way. PTV using a ventilator with a built in refractory period resulting in inactivation of the trigger for some of the babies own breaths enables peak inspiratory pressure and inspiratory time to be maintained and might be more appropriate for weaning infants with chronic lung disease.

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1 Greenough A, Milner AD. Respiratory support using patient triggered ventilation in the neonatal period. *Arch Dis Child* 1992;**67**:69–71.
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Is 28 weeks of gestation equivalent to 1000 g of birth weight?

SIR,—With the rapid development of neonatal intensive care, many tiny and premature babies are now surviving. In 1979 the World Health Organisation published a number of recommendations on the methodology of reporting perinatal mortality statistics[1]: 'It is recommended that countries should present, solely for international comparisons, "standard perinatal statistics" in which both the numerator and denominator of all rates are restricted to fetuses and infants weighing 1000 g or more (or, where birthweight is unavailable, the corresponding gestational age (28 weeks) or body length (35 cm crown-heel)'. These recommendations have been strongly endorsed by the International Federation of Gynecologists and Obstetricians.[2] In the 9th revision of the *International Classification of Diseases Clinical Modification*,[3] extreme immaturity (code 765.0) is defined as 'Usually implies a birthweight of less than 1000 grams and/or a gestation of less than 28 completed weeks', and other preterm infants (code 765.1) as 'Usually implies a birthweight of 1000–2499 rams and/or a gestation of 28–37 completed eeks'. However, these definitions and criteria ay be flawed. The issue here is whether 28 eeks of gestation is equivalent to 1000 g of irth weight. Although the mean birth weight t 28 weeks varies from country to country, ıost of the published data show that infants of 8 weeks weigh more than 1000 g on average, uggesting that 28 weeks of gestation is not a ood surrogate for 1000 g of birth weight references available from author).

Although births with weight around 1000 g r 28 weeks of gestation account for a very mall proportion of total births, perinatal nortality in this group is very high. Therefore, n statistical reporting of perinatal mortality, adoption of different criteria (1000 g *or* 28 weeks) may yield different results. In perinatal research, especially that focusing on preterm births or very low birthweight infants, inconsistency of criterion for sample selection may introduce misclassification into the study, which could bias results in either direction. Thus, only one criterion should be used in statistical reporting of perinatal mortality and perinatal research.

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